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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

December 20, 2006
Marriott Hotel Seatac
9:00am – 4:00pm

Committee Attendance:
Angelo Ballasiotes, Pharm D
Robert Bray, MD
Carol Cordy, MD (Vice Chair)
Alvin Goo, Pharm D
Jason Iltz, Pharm D
Janet Kelly, Pharm D
Daniel Lessler, MD (Chair)
T. Vyn Reese, M.D.
Patti Varley, ARNP
Kenneth Wiscomb, PA-C

Dan Lessler: We can get started here. I'm Dan Lessler. I'm chair of the P&T and I think we're going to begin. First, Jeff Graham has some announcements. Jeff?

Jeff Graham: Well, I just wanted to announce to the public and also to the committee that as you know that we are a member of the Drug Effective Review Project with the Oregon Health Sciences or actually the Center for Evidence Based Policy along with about 16 other states. We are in the process now of finalizing the DERP II, which is the second phase of this project. We will be having…we have scheduled six meetings for this P&T Committee next year. The first one will begin in February and we're staying the third Wednesday of that month. So we have six meetings we have scheduled. We're not certain we will have to have all of them, but we will have those scheduled.

We will be doing a presentation at the February meeting to the P&T Committee about our procedures and so forth for updates. You know we've been asked questions about that and we will be bringing that forward and we will be reviewing what the schedule will be for the year. Another comment is that we'd like for…particularly the pharmaceutical manufacturers that if they have concerns to address to the committee that they would come through the Health Care Authority and we get those to all the committee members. We've always done that and will continue to do so and would prefer that you not bother them in their offices with your concerns because we certainly get to them and we'd like to be transparent and get that to all of them. Otherwise, we're rolling along just fine.

Dan Lessler: Thanks. Also wanted to remind people. I believe, Regina, there is a sign-in sheet for people who want to comment. So if people are planning to make comments today if you could please sign in we'd appreciate that. Is Susan Norris…are you on the phone? So Jeff do you want to…

Jeff Graham: I will see what I can do.

Dan Lessler: Susan Norris from OHSU was going to be joining us for the presentation on the first agenda item.

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* For copies of the official audio taped record of this meeting, please contact Regina Chacon at (206)521-2027 pdp@hca.wa.gov.

Jeff Graham: They were all reminded yesterday.

Dan Lessler: Is that Susan?

Susan Norris: Yes, it is.

Dan Lessler: Hi, Susan, it's Dan Lessler.

Susan Norris: Good morning.

Dan Lessler: Good morning. So we're all keyed up here. We've got your title slide up from your PowerPoint and basically you can just start right in and take it from there and just let us know when you want the next slide.

Susan Norris: Okay.

Dan Lessler: Thanks.

Susan Norris: First of all I got the message about a half hour ago you wanted this shortened considerably. I apologize, I wasn't able to…in that timeframe send you a shortened PowerPoint, but the slides are numbered here and I'll be referring to the numbers and telling you when to jump ahead because I can shorten this significantly. How much time do I have?

Dan Lessler: Jeff…let's see, we've got about an hour and a half or an hour and 20 minutes for the…but we need to do stakeholder comments and our [inaudible] so maybe we should say 20 to 25 minutes or so. Would that work?

Susan Norris: Yeah, that's fine. Okay. I actually planned on shortening it further, but I'll just see how it goes. Okay. So first of all I'd like to acknowledge my teammates on the second slide. The third slide these are usual sorts of search strategies that are exhausted of the English language literature. The fourth slide is inclusion criteria. We looked at [inaudible] stage requests both adults and pediatric populations, outpatients with asthma – exercise induced asthma and COPD. We focused on two long-acting drugs Salmeterol and Formoterol. A number of short-acting drugs, which are listed there two of them, are available only in Canada. I'm going to focus…those are Fenoterol and Terbutaline. I'm going to focus today on Albuterol and Levalbuterol and not discuss Metaproterenol and Pirbuterol for which there was very little data anyway.

The next slide, which is number 5 inclusion criteria. I'll be presenting only effectiveness outcomes, which is what the states had requested that we focus on and those outcomes are listed there on slide number 5.

Okay. Slide number 6, inclusion criteria with respect to study designs. Because of fairly perfuse literature and also obviously the strengths of the study designed we chose to focus only on head-to-head studies and in randomized controlled trials as well as looking for systematic reviews of the drug comparisons of interest. We look at all quality comparison…all quality categories, which we ingrate into three categories, but only focus…our conclusions are based on the fair and good studies.

For adverse events we examine all study designs because observational data and other designs [inaudible] trials are [inaudible] useful here.

Okay. The next slide entitled data synthesis and analysis, which is slide number 7 we were confined really to a qualitative synthesis just because of the diversity or the heterogeneity of outcomes in populations for effectiveness outcomes.

Okay. Slide number 8 starting with the result section here. We had a total literature of over 100 articles head-to-head randomized controlled trials including addressing all of the comparisons of interest including the two Canadian drugs. Here you can see the breakdown with respect to disease entity obviously or not surprising with both studies focusing on asthma.

The next slide is number 9. Here you see the results broken down by comparison. We'll focus on the first two here. These are efficacy and effectiveness studies focusing on the effectiveness…studies with effectiveness outcomes. We had many fewer studies for the first comparisons, Salmeterol versus Formoterol. There were only 9 studies in total and Albuterol versus Levalbuterol 7 studies as is both adults and children combined.

Okay. The next slide, which is number 10 labeled prior systematic reviews. We were not able to identify any systematic reviews that were relevant here. There are several systematic reviews comparing these various drugs to placebos, but no studies with head-to-head comparisons of interest to us here.

Slide number 11 and then I will start in with the key questions. There are 10 key questions and I'll primarily focus on a summary of those results. The first key question addressing adults in the comparison of the two long-acting drugs and then I'll go into the children comparisons, which is key question number 3, which is outlined in slide number 12.

Okay. The results of Formoterol versus Salmeterol in slide number 13. The first population is adults with asthma. We looked at the effectiveness outcomes listed there in the number of studies listed for each of those outcomes and there were no significant differences for the outcomes of symptoms or rescue medications, etc. for the studies; the small number of studies that looked at each of those outcomes in a head-to-head fashion. So for those outcomes we couldn't demonstrate on differences between the two drugs for adults with asthma.

Going on to slide number 14 the same overall long-acting drugs being compared for exercise induced asthma and COPD. Again, not a lot of literature…even less literature here. Only one study looking at exercise induced asthma with a maximal fall in FEV1 and here we did look at pulmonary function just because of the nature of the disease entity and the interest in a short timeframe for treatment of exercise induced asthma. There's no significant difference in maximal fall and FEV1. The onsite of Formoterol was slightly faster, which is [inaudible], but the bronchial dilation before exercise taking the drug and then measuring 5, 30 and 60 minutes after inhalation there was slightly more bronchial dilation with Formoterol.

In COPD there were two studies examining effectiveness outcomes. Here, no significant differences were demonstrated for symptoms, breathing effort and discomfort and dyspnea after treatment.

Going onto the next slide, which is slide number 15 looking at the same two long-acting agents in children with asthma there was only one study. There was a broad range of ages 6 to 17. Here there were many, many comparisons for all sorts of different symptom and other scores and there was no correction for these multiple comparisons. Several of these comparisons came up in favor of Formoterol. One of those was health-related quality of life activity score as scored by the caregiver slightly in favor of Formoterol. The need for short-acting beta agonists use was less with the Formoterol and there were two other outcomes—clinician-assessed night-time asthma severity score that registered…or the results were in favor of Formoterol and the same with that last outcome listed; patient-assessed day-time asthma severity score. There were no significant differences though in a number of other outcomes listened there or frequency of poorly controlled days, etc. So again this study showed a few outcomes in favor of Formoterol, but they examined many, many outcomes without correction for multiple comparisons.

So in summary for key question 1, which is on slide 16 adults comparison of the two long-acting agents for asthma there is really limited evidence of no significant difference between the two drugs. For exercise-induced asthma and COPD there really is insufficient evidence and what there is shows no difference between the two drugs.

Key question 3, which is on page…on slide 17 is the same question, the long-acting agents in children with asthma the one study with multiple comparisons really provides insufficient evidence from which to compare the two drugs.

Going on key questions 2 and 4, which are slides 18 and 19 here we're going on with the short-acting drugs and as I said all focusing on Albuterol and Levalbuterol although there was some data on Pirbuterol and Metaproterenol.

So slide number 20 labeled Albuterol versus Levalbuterol focusing firstly on adults with asthma. There were two trials of relevance. The first was a randomized trial, fairly large, 362 participants. These were given interestingly enough Albuterol and Levalbuterol were given on a regular basis three times a day by nebulizer over four weeks, two different dosages for each of the two drugs and the results were that a rescue medication use was decreased in all groups. Levalbuterol, these are compared to baseline so within group comparisons Levalbuterol 1.25 and Albuterol 1.25…well, Levalbuterol I should say 1.25 had a significant decrease in rescue medication uses as measured in puffs per day. Albuterol 2.5 approached a statistical significance at the .05 level. There weren't between group statistics presented in the study just the within group statistics. The outcomes of asthma or asthma increase, which were not defined in the study. There was no significant difference within or between the groups. A second study of relevance here in adults with asthma was a controlled clinical trial. In other words not randomized, but investigator assigned. A smaller study and here this was a treatment in the emergency room with three doses of each of the two…of one or the other of the two drugs. There was less need for additional treatment after the three initial study drug treatments with Levalbuterol, but there were similar hospitalization rates after the emergency room visit with the two drugs. Although the study wasn't powered to examine utilization outcomes these results were actually appropriately presented by the authors just in the discussion section. So this really isn't that useful of an outcome. It's just really a comment on the similar hospitalization rates in the Nowak study.

Going on to the next slide, number 21. In the other two disease entities exercise induced asthma and COPD no data of note that we can use to compare these two drugs in those populations.

Slide number 22 going on with the Albuterol/Levalbuterol comparison in pediatric asthma looking at…there were four studies of relevance here. The first two that I'm looking at on slide number 22 are the regular use of the nebulizer three times a day over three weeks. The next two studies will look at the next slide where usage of these two drugs was in the emergency room. So on slide number 22, the Skoner slide with fairly lengthy follow up using the two drugs regularly found no significant difference in a number of effectiveness outcomes that are listed there.

The Milgrom study in children 4 to 11 years found no significant difference in several of the symptom score measures, symptom free days, quality of life, rescue medication. [inaudible] the only significant outcome based on it was that the day 14 to 21 there were more asthma controlled days, better control with Levalbuterol I'd say at the lower dosage of .31 compared to the higher dosage Levalbuterol .63 or the Albuterol 1.25 dosage.

The next slide, slide number 23, I'm still on pediatric asthma. As I say there were four studies. These were the second studies…three and four that looked at the usage of these two drugs for acute treatment of asthma in the emergency room. Two studies are listed there. Both these fairly small Hardasmalani children 5 to 21 years where the drugs were…this was a randomized trial both of which the treatment groups were combined with itratropium and there was no significant difference in the clinical outcomes listed there of rescue medication, use oxygen, saturation and respiratory rate. Quereshi looked at children 2 to 14 years and again found no significant difference in the outcomes listed there.

The next slide, slide number 24, we see the same two studies in the emergency room in terms of health care utilization or admission rates from the emergency room and there were no significant differences between the two drugs in either study. Quereshi also looked at length of stay in the emergency room as well as admission rate and again found no difference between the two drugs.

In the next slide, which is slide number 25 this is a third study of pediatric asthma utilization in the emergency room, which was Carl and [inaudible] published in 2003. It was a fairly large study of 547…85% of the population of these children of a broad age range were African American. This was the usual three treatments 20 minute intervals between…of one drug versus the other. Hospital admissions in this study were similar…I'm sorry, were different between the two drugs with a

higher hospitalization rate with Albuterol of 45% and Levalbuterol 36% with a P value of .02. The other outcomes examined length of stay, the hospital, number of treatments in the emergency room and the emergency room length of stay were not different between the two drugs. So this study shows results different from the two other ones—the Hardasmalani and Quereshi study and the Carl study did show a difference in hospitalization admission in favor of Levalbuterol. Looking carefully at these three studies from an ethologic perspective in terms of primarily the potential for bias…these studies were fair quality studies and I couldn't see any major potential influences or sources of bias in any of these three studies where we have some what discrepant results.

Okay. Going on with slide number 26…I'm sorry, we'll skip 26 and 27, which look at the Metaproterenol and Pirbuterol and go on with the summary slide of key question 2, which is slide number 29 labeled key question 2. So adults with asthma or COPD examining the short-acting agents there is really insufficient evidence to draw conclusions about the comparison of these two drugs.

The next slide labeled key question 4, which is the Levalbuterol in children we have no significant difference in symptoms between the two drugs in two studies examining regular usage to three times a day or end in two studies examining two drugs in the emergency room. In two small studies hospital admission from the ER did not differ significantly between the two drugs in the larger study predominantly of African American children. There were lower rates of admission with the Levalbuterol.

Okay. Going on with key question 5 and key question 7, which are outlined in slides 31 and 32, starting where we are examining adverse events with the long-acting…the two long-acting agents.

Going on with slide number 33, Salmeterol versus Formoterol in adults. Withdrawal rates were similar among the studies that are the range of rates as listed there and the number of studies…so similar rates of total withdrawals and withdrawals due to adverse events between Salmeterol and Formoterol in adults.

I'm going to skip here to the summary slide, which is slide number 39 labeled key question 5. So adults comparing the two long-acting agents with respect to adverse events, as I mentioned, withdrawal rates total and due to adverse events were similar between Formoterol and Salmeterol. Cardiovascular adverse events there was an increase in the palpitations in heart rate in a small number of studies in Formoterol compared to Salmeterol. Potassium decreased more with Formoterol in one study, but there were no statistical comparisons in that study and the number of patients with both of these either cardiovascular events or the decreased potassium was small in the studies that examined these outcomes. Other side effects had headache and tremor. There was no significant difference between the two drugs.

Summary slide of key question 7, the same comparison of long-acting agents in children. There is really insufficient data to draw comparisons here. Withdrawal rates were similar in the studies that reported that and severe adverse events were not reported in any of the studies we identified.

Okay. Key question 6, which I've outlined in slide number 41, adverse events in the short-acting agents—Albuterol and Levalbuterol in adults and the next slide, number 42, the same question in children. So going on with the examination of adverse events in adults with the short-acting agents, which is slide number 43. Total withdrawals – only one study reported those data in adults in a four-week study and the withdrawal rates are listed there. 5.4% with Albuterol, 2.5 Levalbuterol. The 4.1% was with the .63 mg dosage and the 10.9% withdrawal rate over four weeks was with 1.25 mg Levalbuterol. This was with the drug used regularly over four weeks. The other studies that reported withdrawal rates were the emergency room, you know, very short-term studies where there was no attrition from either group during their emergency room stay.

I'm going to skip to the next few slides to slide number 46. It is labeled Albuterol versus Levalbuterol in children. Withdrawal rates were only examined in two studies and were similar between the two drugs.

Now I'll go into the two summary slides and adverse events, which are first of slide number 49. Adverse events in adults with asthma comparing Levalbuterol and Albuterol there were no significant differences in the increased heart rate 2 to 5 beats per minute with both drugs. Decreased potassium was noted in one study and nervousness and tremor and increased blood sugar were noted at similar rates between the two short acting drugs in adults.

The next slide, slide number 50, the same adverse events with the short-acting agents in children. Similar results to adults; the heart rate increased with both drugs with no significant difference between the drugs. Blood sugar increased with Albuterol more than Levalbuterol in one study and decreased in potassium was noted and in the short term in both drugs, but no significant difference between the two drugs.

Slide number 51 starts the last two questions examining the data on these various drugs and subpopulations. I see question 9 there of slide number 51. We're looking at demographic characteristics, co-morbidities, etc. in the long-acting agents and in slide number 52 a similar question of subgroups in the short-acting agents.

So what we found with respect to subgroups starts on slide number 53 labeled subpopulations: sex and age. We weren't able to find much data on subpopulations that was really helpful. Although not surprisingly the COPD studies were largely in male populations and those studies were…the results were not stratified by sex in any study, but the studies that were predominantly male the results were consistent with studies that were more balanced with respect to sex. 65 and older, the older populations no studies specifically examined older adults. The mean age in four studies was over 65 and those results were consistent with the overall data in studies that encompass younger populations, but again no stratified analyses on age in any study.

Next slide, number 54, subpopulations with respect to race. This is the…actually, the next two slides look at emergency room use of Albuterol versus Levalbuterol in children and were predominantly African American populations. This is the Carl study and the Quereshi study and as I mentioned previously the Carl study was the study that showed a decreased hospital admissions with Levalbuterol versus Albuterol and the Quereshi study showed no significant different in admission outcomes as well as other outcomes as symptoms between the two drugs. So these are the only studies that focused on racial minority and there were no stratification of any of these studies based on race.

The next slide, slide number 56 talks about comorbidities. There was almost no data addressing comorbidities. Obviously the COPD studies encompassed a number of patients with a number of comorbidities, which were often just listed, but didn't enable one to look at specific comorbidities in single or combination fashion. The only study with any data was Cozzola in 1998 who examined 12 COPD patients with pre-existing cardiac arrhythmias and he noted a greater increase in heart rate with Formoterol compared to Salmeterol and that should say a PE less than .05, but again this is a small…a very small study and only a single study.

So in summary on subpopulations, slide number 57, entitled key question number 9, the one study that I mentioned in COPD and no other data are really helpful with respect to demographic characteristics, gender or comorbidities and in children the summary slide, slide 58, key question 10 subgroup characteristics and children just the two studies that were predominantly African American children in the emergency room comparing the two short-acting agents one of which…one study of which showed a difference in hospitalization, but again this was also not stratified by the demographic characteristics of interest

So the last slide, again, I'd like to acknowledge the team that helped me with this report. Thank you.

Dan Lessler: Susan, thank you. That was really very good, very helpful.

Susan Norris: Okay. I could hope you could follow the slides. I'm sorry, I was asked to shorten it without being able to send you the new copy.

Dan Lessler: No problem. Actually, what I wanted to do here with you on the line is first just open it up to questions from P&T Committee Members to you regarding your presentation.

Vyn Reese: Hi, this is Dr. Reese and I had a question about why you didn't mention observational studies regarding safety of long-acting $beta_2$-agonists? There are some studies suggesting that there is an increase morbidity and mortality with long-acting $beta_2$ agents and there have been several warnings regarding that class of drugs and I'm curious as to why you didn't include that in the review?

Susan Norris: Yeah, observational data were included with respect to…yeah, observational data or in other words non-randomized study designs or non-trial data were included if they were head-to-head data. So the states that asked us to compare the two long-acting agents together we did not examine the question of whether long-acting agents compared to short-acting or compared to other asthma treatments increased mortality. That wasn't a question we were asked. We looked only for head-to-head data and there weren't observational data that are helpful there comparing the two drugs with respect to the outcomes that you mentioned.

Vyn Reese: It seems like it's pretty important to know whether the class is a risk.

Susan Norris: Yeah, again, if they don't ask us to answer that question we don't.

Vyn Reese: Right. Okay. That just seems to me that that's an obvious question to ask.

Susan Norris: Yeah, I agree.

Vyn Reese: If you have head-to-head data you need to know that the class as a whole is safe and how much we should promote it.

Susan Norris: Right. And this question was raised by…I don't recall which state, you know, after the key questions that we review were approved, but, you know, again, if we're not asked to review a question we don't.

Dan Lessler: Another question?

Bob Bray: This is Bob Bray. The question for you on the Carl study that showed the decreased admission rate in the Levalbuterol group. Were there follow up studies that identified over what period of time they looked for subsequent hospitalizations in both of those groups?

Susan Norris: Um, no. That was not part of that publication and I, to the best of my knowledge, and we would have picked it up at least if it was prior to our search kind of off…there were no follow update on that study. And the authors finished that study, you know, their last paragraph is this, you know, interesting results needs to be replicated and needs to be further follow up data are needed. But I'm not aware that those data have been published.

Dan Lessler: Other questions from committee members? Susan, would you be available just to stay on the line here a bit? We have some stakeholder comment and we have found it useful in the past just to have the OHSU expert on the line because sometimes issues come up.

Susan Norris: Sure. Okay. I'd be happy to. I do have to leave by 10:00.

Dan Lessler: I think we should be able to do that. If you could just hang with us. I have four people listed to speak. First is Dr. Marvin Wayne and I would ask if people could, in addition to just identifying yourself, let us know whether you are here representing any company or if you're being paid for your comments. Thanks.

Marvin Wayne: Good morning. My name is Marvin Wayne.

Dan Lessler: I'm sorry, Doctor. The other is the limit is three minutes and we'll stick to that pretty closely. So I will cut you off after three minutes.

Marvin Wayne: I'll duck the hook as it comes through. Good morning. My name is Marvin Wayne. I'm an emergency physician and have been practicing similarly for almost 34 years in Bellingham. I am the medical director for the Medic One system for Bellingham and Whatcom County and I'm an associate clinical professor at the University of Washington and I want to thank the committee for the privilege of being here and speaking and I represent myself.

Approximately two years ago as the director of the Medic One system and the system that covers 2,200 square miles up north where we have dodged the second wind storm and hopefully will dodge the third today. We have a problem of distance of transport and a lot of patients by the time they call us have been sucking away on whatever beta agonist they are using, if any, for a great period of time. So we see a significant side effect profile issue. Because of that we decided to evaluate Levalbuterol based on some work done by a colleague of mine, Richard Nowak, in Detroit. For almost two years now we've looked at approximately 400 patients of which we did some detailed analysis on about 180 and what we say contrary and with due respect to the wonderful work the folks in our sister state of Oregon have done is we have seen a significant differential and side effect profile whereas the patients typically after they would get additional Albuterol therapies from us would be extremely tachypneic tachycardic…tachypneic related to the disease hopefully gradually improving the tachycardia, the jitteriness, the side effect profile in 180 most recent patients we looked at and again observationally we saw an improvement.

Additionally, as we began to evaluate the drug in hospital and looking at the cost differentials of the HFA we're finding that we're dealing with almost a non-existent cost differential. In fact, my pharmacist informed me yesterday that the hospital pays less for Levalbuterol HFA than they do for Albuterol HFA. The additional costs that we're seeing now are the hydrofluoralkane as opposed to the chlorofluorocarbons, which are being eliminated because of their ozone destroying opportunities.

Asthma, unlike most disease over my career, which is almost 40 years in medicine, is a disease that's increasing. Time does not allow us to discuss why, but it is increasing. It's a disease that when I go to treat my responsibility to patients is to do the very best thing for every patient, to have the option to individualize where I need to individualize. I need every tool to do that. We are not cost effective if we don't provide good care. We are not efficacious if we don't have options. If we were talking about thousands of dollars of differential then maybe we could address the cost-effectiveness, but we're talking about pennies in the nebulization. We're talking about near equivalencies in the MDI's. Please, as a clinician and I ask you this as a clinician, add Levalbuterol as well as Racemic Albuterol to your PDL formularies. Give me that option. It will help me to be a better doctor. More important, it will help patients to have a better day. Thank you very much.

Dan Lessler: Thank you. Any questions?

Susan Norris: Can I make a comment?

Dan Lessler: Yes, please.

Susan Norris: Dr. Wayne I would urge you to publish your findings. We can't review them if they're not in the public domain. That's very interesting and I urge you to publish them.

Marvin Wayne: Thank you. I appreciate that comment. We've looked at that issue. Unfortunately, at the moment we're in the middle of an NIH study on cardiac arrest and because of limited resources that's sort of where all mine are going, but I would agree with you. When that study is completed in a year and a half we're going to collect the data and publish it as an efficacy, we hope, side effect profile. We don't have the outcome data to look at what happens down the road right now, but again your point is very valid and I was very clear in stating this is observational, but I think it is an important observation and in my many years in medicine sometimes our eyes, our ears and our feelings are often better than anything that we have. So thank you for your comment and thank you to the committee allowing me to be here.

Dan Lessler: Thank you. Next is Ms. Jennifer Stoll from…

Jennifer Stoll: Good morning. My name is Jennifer Stoll and I'm the government affairs director in Washington for Sepracor Pharmaceutical. We make Xopenex brand Levalbuterol. I'm here today to speak about the change in the market that's occurring between the CFC's and the HFA's. The change that is being occurred because of an FDA policy statement to remove the CFC, the chlorofluorocarbons from the market effective December 31st, 2008. I'm passing out to you right now an FDA statement that says that Sheering Pharmaceuticals who produces the U.S. supply pretty much of the CFC's has announced they are going to stop their production by spring of 2007. This is going to put a massive problem on the shortages of CFC's to the United States. No other generic manufacturer is going to be able to pick up that supply because the EPA has decided that they're not going to allocate out any more CFC propellant to any other generic manufacturer to allow them to do it. So this transition to HFA propellants is happening today.

HFA propellants only represent less than 10% of the current utilization within the Medicaid…within the State of Washington Medicaid and I would encourage the P&T members to please look at what other states are doing, what your neighbor states are doing—Idaho, Nevada, Texas, California have all added HFA alternatives including Levalbuterol HFA to their PDL to encourage this transition to happen today.

In support of my testimony I'm also passing letters from various state legislators who are very concerned about their shortages in their districts and they would like to encourage all of you to add all of the FHA alternatives to the PDL. Also, I've also included a package of letters from physicians throughout the state who are also encouraging you to add Xopenex HFA to your PDL and for this reason I thank you for today and encourage you to add all of the HFA alternatives to the PDL today. Thank you.

Dan Lessler: Thank you.

Jeff Graham: This is Jeff Graham. I'd like to make comment. I think probably your company is new to this process. We do not accept any information today although that needs to be either mailed in to the Health Care Authority or submitted to the Oregon Health Sciences at the Center for Evidence Based Policy. So we will not accept that today and if you want us to, we can hand it out later.

Dan Lessler: Okay.

Jeff Graham: We do have letters already that our members have seen. So they are in the packet they have.

Dan Lessler: That's correct. Next is Dr. Meredith Zarling.

Meredith Zarling: Good morning. Thank you for the opportunity to speak to you today about Serevent and Ventolin HFA. Thank you for that. My name is Meredith Zarling and I'm a clinical pharmacist as well as a regional medical scientist for GSK. Serevent discus is indicated for the long-term maintenance treatment of asthma for exercise induced bronchial spasm and for the prevention of bronchial spasm in patients with COPD. It's approved for adults and children 4 years of age and older and has a convenient dose counter.

Since long-acting beta agonist use of asthma may increase the risk of death, Serevent should only be used as additional therapy for patients not adequately controlled in other controller medications such as inhaled corticoid steroids, or if the patient has disease severity who clearly warrants use of two maintenance therapies.

The gold guidelines for the treatment of COPD recommend inhaled long-acting bronchial dilator therapy for patients whose FEV1 is less than 80% predicted. The American Thoracic Society and European Respiratory Society guidelines state that data from trials using concomitant long-acting beta agonist and inhaled corticoid steroids show a significant additional affect on pulmonary function and I just wanted to briefly show you how quickly and easily the Serevent discus can be used compared to other inhalers that require removing capsules from packaging. Everything is fully contained in the discus device. It's three easy steps. You open it, you click [end of Side A]

[Side B] …restriction of COPD and asthma together with an inhaled corticoid steroid are recommended in national guidelines and then I also wanted to talk about Ventolin HFA very quickly. As you know, it's a short acting beta$_2$-agonists. It's indicated for treatment or prevention of bronchial spasm for adults and children greater than 4 years of age. Ventolin HFA is the only brand that has a dose counter that's available on the market. It provides patients with the ability to know how many doses remain in their rescue inhaler and very importantly this can keep them from finding it empty during an asthma exacerbation. Based on the data and national guideline recommendations Serevent and Ventolin HFA should remain available to Medicaid patients in Washington on an unrestricted basis. Thank you very much for your time.

Dan Lessler: Thank you. Any comments or questions? No? Okay. Thanks. Next is Dr. Dan Manning.

Dan Manning: Hi. I'm Dan Manning with Shering-Plough Global Medical Affairs and I'm one of three directors. I'm here to make a few comments about Proventil HFA. As you've heard from the OHSU report that most of the short-acting beta agonists really clinically are very similar. What makes Proventil HFA different is it is one of two products on the market with an age indication down to four years of age and an indication for exercise induced bronchial spasms. Also these two products with the same indication has no patient restriction for storage on it.

And the other comment I wanted to make in regards to the phasing out of the CFC is Shering-Plough has in full production the HFA production so there will not be a shortage problem when that comes out. We've started all of the productions in place right now. Thank you.

Dan Lessler: Thank you. Any questions? I'll just ask the committee again if there are any final questions for Susan Norris here before we…all right, Susan, thank you very much for your time and for staying with us.

Susan Norris: Uh huh. Thanks very much.

Dan Lessler: Take care. Bye bye. So as I think we've become accustomed to doing maybe we could just begin with some general observations and discussion. I'm thinking that it might be easiest if we split this out into the short-acting/long-acting and maybe we should start with the short-acting agents first.

Vyn Reese: This is Dr. Reese. On the studies that we have to review it doesn't look like there is any difference in the short-acting agents that, you know, in the published literature. So I think we have to assume that they are equivalent based on what we know today and then there are all sorts of questions of availability, but the drugs are equivalent so there's not really much difference between them. That would be my take on the issue for short-acting drugs.

Dan Lessler: Alvin, did you have a…

Alvin Goo: No, I agree.

Dan Lessler: Siri , I was wondering if I might ask you just to comment on HFAs and CFCs and assume…with CFCs going away clearly there's going to have to be…it's going to have to be HFA.

Siri Childs: What we've done right now for Washington Medicaid is that right now everything is covered and what we've done is we've made the price on the HFA equal to the pharmacists acquisition cost so they're not penalized if they have to use the FHA product. We've recognized that there could be a shortage although we haven't really experienced it yet in Washington.

Dan Lessler: Okay. Any other comments or observations about short-acting agents? It sounds like, you know, Vyn had mentioned that from the review we've seen and what we've read with respect to short-acting there does not seem to be much in the way of significant clinical differences either in terms of effectiveness or safety. I don't see anybody disagreeing with that. So is…would anyone be willing to maybe put forth a motion of some sort for starters here? This is our first time reviewing this class. So we don't have a previous motion to look at. We could look at our standard template to get started here.

Bob Bray: This is Bob Bray. I would just suggest that we make two separate motions—one for long-acting and one for short-acting.

Dan Lessler: Yes. So maybe we can begin with the short-acting here if that would be…

Vyn Reese: This is Dr. Reese. I'll make a stab at it. Now some of these drugs aren't available in this country. Some are the Canadian drugs. So we need to make sure that we don't, you know, they're included in the review. We want to make sure they're not in the motion.

After considering the evidence of safety, efficacy and special populations for the treatment of asthma and chronic obstructive pulmonary disease, I move that Albuterol, Levalbuterol, and Metaproterenol, are safe and effective. No single agent is associated with fewer adverse events in special populations. These drugs can be subject to therapeutic interchange on the Washington Preferred Drug List for the treatment of asthma and chronic obstructive pulmonary disease.

Man: I don't think Pirbuterol is available.

Woman: It is.

Vyn Reese: It is available? Okay. Include…add Pirbuterol to that list.

Alvin Goo: Hi. This is Alvin. I'm wondering if we need to also include some sort of stipulation that it needs to be in a certain formulation nebulizer and meter dose?

Dan Lessler: So how do you…where do you want to add that, Alan? Just at that…right after the listing of the drugs there?

Alvin Goo: Yeah.

Woman: What do you want to include?

Alvin Goo: That it should include a nebulizer and meter dose formulation. I'm sort of hesitant to add oral because it's typically not recommended and not well used, but I'll leave that up to you to decide if you want to include oral or liquid, but I would…

Man: It wasn't included in our study.

Alvin Goo: No? Okay.

Patti Varley: This is Patti Varley. For pediatric use sometimes.

Alvin Goo: Right. That was the liquid that I was referring to. It's usually not recommended, but there might…in a few cases.

Dan Lessler: And it wasn't really reviewed either. So I think we should…

Alvin Goo: Okay.

Man: So should we add a point in there about an HFA product?

Dan Lessler: The question is should we add a point about having an HFA product?

Vyn Reese: Pretty soon they are all going to be HFA. I mean it's a matter of law. So we have to have HFA products because there aren't going to be any others.

Dan Lessler: Siri , did you want to comment here? Did you have a comment about that?

Siri Childs: Not really. The HFA products are the ones that we are going to go forward with in the future. So, you know, we're going to be looking at them and their competitive prices.

Man: It wouldn't be necessary to include in our motions…

Siri Childs: It will be required.

Dan Lessler: Right. Right. Okay. So the mo…is there a second I should say? Ken, second. Okay. Vyn, if you want to read it one more time.

Vyn Reese: Just bring it back down so I make sure I've got all of this. After considering this evidence of safety, efficacy and special populations for the treatment of asthma, exercise induced asthma, or chronic obstructive pulmonary disease, you know, I don't know if we should spell those out or if that is understandable. I move that Albuterol, Levalbuterol, Metaproterenol, and Pirbuterol and safe and effective. The Washington Preferred Drug List must include a nebulizer and a metered dose formulation. No single beta agonist is associated with fewer adverse events in special populations. The short-acting beta agonists can be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of asthma, EIO or COPD.

Dan Lessler: Okay. So that's the motion on the table. Any further discussion? Okay. All those in favor, please say, I.

Group: I.

Dan Lessler: Opposed, same sign. All right. So next we can take on the long-acting beta agonists and again just beginning with any observation or comment that people have.

Vyn Reese: This is Dr. Reese. I'm concerned that the safety of this class was not reviewed or commented on. There has been a lot of recent publicity about this that maybe…the drugs would be used as a second line, clearly as a second line agent and in larger observational studies there are safety issues. So I don't know how we can say that. There are though indications for these agents, as well. So they need not to be the first thing you reach for single treatment for asthma. That's the real concern. And so that's my…I don't think there's any difference between the two drugs that were reviewed. I don't think there's any…we don't know if one is safer than the other and we don't know exactly why the safety issue has come up precisely. I think it's an area of concern and a question mark at this time with the available evidences as to how safe this class as a whole is and it certainly should not be promoted as first line therapy.

Dan Lessler: Other comments about that?

Alvin Goo: One here.

Bob Bray: I guess I would just suggest based on what Vyn just said that we ought to ask for that to be a key question next time it comes up for review and see if there is more evidence at that point that might help in that regard. And I think I might have mumbled a second that you could put me down for that on this last motion.

Dan Lessler: Okay.

Bob Bray: I could tell you weren't sure.

Dan Lessler: I would just comment that I agree that certainly there is increasing concern based on observational studies although it's a complex issue to tease out in terms of the confounding and so forth. At this point the national guidelines have not been modified, you know, in terms of the recommendations, which would not have…I mean national guidelines would not have you starting somebody on a long-acting. They would have starting somebody on a controller, but it's something that could change in the future depending. Any other…

Janet Kelly: This is Janet Kelly. I think in my mind it's like…it is a reasonable treatment option for certain cases and for us to not, you know, it's like how are we going to deal with this when the guidelines have not? We're going to have to trust that, you know, they are being used as a second line agent and

then our business is what do we…does it matter which one we choose at that point? So I think it's a good idea to consider it in the future, but for today I think we need to move forward with if this is an appropriate therapy, does it make a difference which one they pick?

Dan Lessler: Right.

Vyn Reese: This is Dr. Reese. I agree. I don't think there's one that's been shown to be safer than the other and it's going to be hard to make our recommendations given the…sort of the prosody of evidence, but there have been warnings sent to patients and these drugs have been withdrawn from some patients because of these concerns. So it certainly is an issue. I don't know how we can craft that into our motion though.

Alvin Goo: Hi, it's Alvin. I also echo your concerns and I'm wondering if it would be reasonable, in the statement, to say long-acting beta agonists should be second line, not used alone and then start there. I don't know if that's allowable.

Vyn Reese: I think that's one way to get around it except the only problem I see with that is for exercise induced asthma for somebody who is an endurance athlete or something running a long race like a marathon or something. They may benefit from a long…that's about the only type of person I could see would really fall into used alone category.

Dan Lessler: Janet, I don't know if you have any response to that in terms of the thought.

Janet Kelly: No. I can't imagine how many endurance marathon runners we have here. I don't think that's probably worth slowing down the process. That seems fine to me.

Dan Lessler: All right. So…any other comments or observations about the long-acting beta agonists? Okay. Is there a motion?

Bob Bray: I'll take a stab at it. This is Bob Bray. After considering the evidence of safety, efficacy and special populations for the treatment of asthma, EIA or COPD, I move that Salmeterol and Formoterol are safe and efficacious. No single long-acting beta agonist is associated with fewer adverse events in special populations. These drugs can be suggest to therapeutic interchange in the Washington Preferred Drug List for the treatment of asthma, EIA or COPD.

Vyn Reese: This is Dr. Reese. What about Alvin's…how did you want to craft that, Alvin, to say, you know, to put your concerns in?

Alvin Goo: Well, yeah, this will be the first time we would do this that I know…I just want to know from Siri 's point is it necessary? Because there are sufficient warnings. But to make our point stronger is it necessary and is this acceptable?

Siri Childs: The way that Medicaid would operationalize that would be of course to use our expedited prior authorization or in our new computer system we would look for, you know, use of another drug. So you tell me what you want to do and we'll be able to do it either way.

Bob Bray: Bob Bray again. As the person taking a stab at the motion I guess my bias would be that given the evidence I think we can state this in the…in our motion and I would prefer to let the guidelines and other recommendations help in choice of drug as opposed to increasing the hassle factor for patients, physicians and pharmacists to have to go through prior authorization to use a drug that we do have an indication for. So my suggestion is that we not put that in.

Dan Lessler: I mean I…personally I tend to agree with you, Bob. I get concerned about actually being more directive than that. Obviously…as with all of the medicines we consider that a lot of them are…there are national guidelines that have been developed, evidence-based that sort of describe their appropriate use and those are always subject to change and, you know, so I get a little bit concerned when we're jumping in in this kind of way. Are there any other comments? Is there a second?

Janet Kelly: Janet Kelly, I'll second it.

Dan Lessler: Okay. All those in favor, I.

Group: I.

Dan Lessler: Oppose, same sign. Okay. The motion passes. I think what we could do now is just take our break a little bit earlier and then come back and do the last…

Man: Yes, and I'll see if we can get our presenter to come a little bit earlier.

Dan Lessler: Do you want to say 25 after the hour?

Man: Yes and I'll make an announce if we can't do it.

Dan Lessler: So we're adjourned until 25 after 10.

All right. Take it from there.

Marian McDonagh: All right. Thank you very much.

Dan Lessler: Thank you.

Marian McDonagh: Okay. So this is an update. The update was completed in May of '06 and so if we go to slide 2 just a general slide about searches and the only thing I wanted to mention is that the searches for this ended in October of '05 and through public comment we did have some new studies added, but generally most of the studies were up through October of '05. So if we move through the next few slides these are our usual slides on our methods. So slide 3, slide 4 is inclusion criteria, and then slide 5 is the interventions and here I wanted to mention between update…the original report and update one the decision was made to not include the drugs there listed at the bottom half of the slide. That they were not actually contributing a whole lot to the evidence and actually making it more difficult to read the report. So this report focuses on those drugs at the top, the stimulants as well as Atomoxetine.

Woman: I'm sorry, I don't mean to interrupt, but the visual display that's up on the projector is missing slides completely. So you need to follow through with your paper printed out slides.

Dan Lessler: I was actually following along…so you're on slide?

Marian McDonagh: I was on slide 5.

Dan Lessler: Yeah, slide 5. And what we have projected is slide 7. So Marian you just continue. We have paper copies of your slides. It would help if you could actually just let us know each time you move forward what slide number you're on or you want us to be on.

Marian McDonagh: All right. I'll do that. So then moving on from slide 5, slide 6 is the outcomes measures that we considered and then on slide 7 is the beginning of the results. So here we have a summary of how many studies are in the review, 262 total. However, in this update there are only two head-to-head studies that were added. We also added a variety of…a large number of placebo-controlled trials. Most of those again being methylphenidate placebo-controlled trials. So now if we move on to the next slide, slide 8, this is not new. This information is…summarizes the concerns we have about the body of evidence in general. So I'm not going to belabor those points. We've talked about them in the past.

On the next slide, slide 9, this talks about the generalizability issues. There are several problems with this body of evidence in that it is focused on a pretty narrowly defined population and we don't have information about the ADHD subtypes within that population that were studied in these trials or other types of studies.

Then we move on to slide 10 and slide 10 is a summary of the evidence in terms of the head-to-head trials and now we have…everything is split up by children, T for adolescents and A for adults. So you can see the bulk of the studies are comparing the various products to the immediate release methylphenidate and a few scatterings of studies elsewhere.

Now move on to slide 11. This is the evidence for methylphenidate comparing the immediate release and any of the extended release products. And here this slide there's really nothing new. One slide…one trial was added to this group, this body of evidence; however, the product that was studied in that trial is called Meta Connect (?) and it's currently not available in the U.S. The findings from that trial were not different from the findings in these other trials in that differences between the products for efficacy were not found.

So if we go to the next slide, slide 12, this is comparing sustained release formulations to each other. Previously we had one trial, which was the Ritalin LA compared to Concerta that found differences on some efficacy measures, but not all. Now we have a new trial. We added the Comacs study, which is Metadate CD versus Concerta. So at the bottom of the slide there there's a bullet that describes the findings from this study. The differences here were based on pharmacokinetics. In the morning Metadate CD was superior to Concerta. In the afternoon the drugs were not differentiated and in the evening Concerta was superior. Adverse events for both studies the drugs were not…differences were not found.

Now if we move to slide 13 dextroamphetamine versus methylphenidate there's no new evidence here so unless you ask me to I won't go into detail on discussing these slides where there is nothing new. Is that acceptable?

Dan Lessler: Yes.

Marian McDonagh: Okay. So let's move to slide 14. This is amphetamine mixture so Adderall versus methylphenidate. Here there are only two trials and again there is nothing new for this body of evidence.

Move to the next slide we had a single study previously that compared multiple drugs and there are no other studies like this. So nothing new to add on this slide.

Move to slide 16, other stimulants. Here we do have one piece of information added. In the previous report Dexmethylphenidate there was no published trials. There was only information we could get out of FDA documents. Now one of those placebo-controlled trials has been published and Dexmethylphenidate was superior to placebo. Anorexia rates were higher for Dexmethylphenidate than placebo. So that's the only thing new on this slide.

If we go to slide 17 this is an old slide as well. There is nothing new added here. This is a summary of all the findings from the MTA study as well as other longer term studies evaluating the duration of effect, how long the effects are seen. What we recorded previously is that the MTA study seemed to show a better continuation of effect over time, which may be related to the higher dose, the more aggressive dosing in that study. So nothing new on that.

Moving to the next slide, slide 18, non stimulants versus methylphenidate and this is the immediate release. This is the Atomoxetine data and I apologize, there are two studies that I failed to add to this slide. One of them was rated poor quality. It's called…the trial name is Focus. It was Atomoxetine versus Concerta. We considered it to be a problem for multiple reasons. It's an open label trial, it was quite large, over 1,000 patients, but there were differences at baseline and randomization was not described and even more concerning is that there was no description of attrition or the number of subjects who were actually analyzed. So we didn't want to report on that study.

The next study was a study called Start, which compared Adderall XR to Atomoxetine and in this study using the scamp scale the Adderall XR was found superior to Atomoxetine on deportment scores, which was the primary outcome measure. Also on attention scores and the proportion of children responding. That was a fairly good size trial, 215 subjects.

Now moving on to the next slide we're getting into…this is slide 19. We go into the evidence on adults and here there's really very little new. The only information we added in the update were four new placebo-controlled trials. They were all trials of methylphenidate.

Now if we move to slide 20 there were no…there's no new information here. This is a summary of the head-to-head trials that were previously found.

Move to slide 21 looking at long-term outcomes. This is evidence that we had presented previously. So nothing new here.

Slide 22 looking at response rates from the placebo-controlled trials here the only thing that has changed or that should change is the methylphenidate information. One new study was added to this information and it's actually not reflected on the slide. This was a study in patients who were comorbid for cocaine abuse and the response rate was lower in this study than in others. It was 38%. So the range on methylphenidate at the bottom of the slide should be 38% to 78%.

The following slide is information about other outcomes and there is nothing new added here.

Moving on to slide 24 adverse event rates…here the trial that I just talked about in cocaine abusing patients the information…data from that study added to the rates for insomnia and appetite suppression, but overall no differences in terms of…there were still no differences between the Modafinil and Dextroamphetamine.

Now moving on to slide 25, indirect comparisons. These are odds ratios that were calculated from the evidence from the different trials…the really small numbers of trials for each drug. For methylphenidate we were able to add information from one trial for each of these: sleep disturbance and appetite disturbance. Change the odds ratio slightly, but it didn't change the overall impression that the odds ratio…the 95% confidence intervals all overlap and with such a small number of trials per drug it's very difficult to make any solid conclusions from this evidence.

Moving on then for long-term safety on slide 26 there were no new studies added for that.

Slide 27 is weight change in children. Again, no new evidence.

Slide 28, height change in children. No new evidence.

Slide 29 looking at subpopulations. Here we have no new evidence in children on slide 29.

No new evidence on slide 30, which is going into gender and also looking at subgroup analyses of psychiatric illness and Atomoxetine. That was all presented in the original report.

Likewise on slide 31. Actually, we did have some new information added for the mental retardation and developmental delay, but it was very, very similar to the previous information and doesn't change the conclusions on the slide.

So then on slide 32 at the bottom of the slide we've added the substance use disorder in adults, which was again primarily cocaine dependence. Methylphenidate resulted in superior response rates compared to placebo in this population and as I said earlier the response rate was 38%, which is lower than what you would see typically in a population not comorbid with substance use disorder.

So overall not a whole lot new in this report, but a quick summary there of what we found. I'm happy to answer any questions.

Dan Lessler: Thank you Marian. I will open it up to committee members for questions for Marian.

Angelo Ballasiotes: This is Angelo Ballasiotes. Say, there's a new delivery system out with methylphenidate called Daytrena.

Marian McDonagh: Right.

Angelo Ballasiotes: Are you folks going to be…

Marian McDonagh: We…yes, that was approved right after this report was finalized. So it is not in here, but we…just recently the decision was made to update this report again. So certainly that is the information we will be going after is to add the data for Daytrana and anything else that's new.

Angelo Ballasiotes: Thank you.

Marian McDonagh: Uh huh.

Patti Varley: This is Patti Varley. Now my understanding is Modafinil was pulled from its approval for ADHD?

Marian McDonagh: Right. The way that the documents read on that is that it was sent back. So it's unclear right now whether they are going to resubmit, you know, maybe do some more studies and resubmit or just discontinue pursuing that.

Dan Lessler: I just want to bring up to that point then that Modafinil is not one that we're considering today so people know for that reason.

Alvin Goo: Hi, my name's Alvin. We sort of segregated Atomoxetine as a non stimulant…what was the reason we did not include studies with Bupropion or other non stimulants?

Marian McDonagh: Well, that's a very good question. I think that from the discussion that was had with the group and actually maybe just to contribute to this, but I think that the group that was making the decision on which drugs to include felt that they didn't have enough use of Bupropion for this or maybe there weren't able to differentiate the use. So they were less interested in reviewing that evidence for this particular update. Maybe that will change in the next update.

Jeff Graham: Marian, I recall too that we…this is Jeff Graham, that we discussed this…wasn't it that we looked at this in other classes and so we weren't certain if we needed to then bring it into this class because most of us had already dealt with it already. I think that was part of it, too.

Patti Varley: This is Patti Varley. Yeah, my recollection was that we had…people had access to that medication via its designation in a separate drug category.

Jeff Graham: Okay. But I don't know when I see Strattera as a non-stimulant in my preferred list I'm wondering if that excludes or promotes the use of that versus not, you know, recognizing that there are other non-stimulants that have been studied and that are effective. I just wonder if that biases prescribing habits and that does concern me.

Marian McDonagh: We also received public comment on that issue and in particular not only Bupropion, but also the tricyclic antidepressants.

Jeff Graham: Right.

Marian McDonagh: You know, some people who are experts in the area of ADHD felt that the report ignored that body of evidence.

Patti Varley: This is Patti Varley again. I think too there is primary treatment and secondary treatment and I think you are also looking at drug classes. So for me in my mind when I think of tricyclic antidepressants or Wellbutrin they are classified as antidepressant medications. They do have a cross indication for ADHD. In this case my understanding right now is the FDA approval of Strattera or Atomoxetine is for ADHD. Now there is discussion about whether they are going to go for a secondary indication for something else, which would reclassify it, but that was at least my recollection in our initial discussion about what to include or exclude leaving it to the clinicians with expertise to know what their secondary options were, still having access under other categories.

Dan Lessler: Are there other questions for Marian at this point?

Alvin Goo: Marian, it's Alvin again. Are there any studies that you're aware of with the stimulants being used in dual diagnosis patients with ADHD?

Marian McDonagh: Sorry, Alvin, I couldn't quite hear the last part of that.

Alvin Goo: I'm wondering if you're aware of any studies with stimulant agents in the subpopulation of dual diagnosis with ADHD.

Marian McDonagh: So dual diagnosis with what comorbidity?

Alvin Goo: ADHD.

Marian McDonagh: ADHD with…

Alvin Goo: And the use of…and studies using stimulant agents?

Angelo Ballasiotes: Angelo Ballasiotes here. The dual diagnosis…what he's meaning, I think, is substance abuse and ADHD. There shouldn't be any stimulants being used in these people at all.

Marian McDonagh: Right. For people who have substance abuse disorder as well. Right. And there's very little evidence on that that we were able to include in the report using our criteria. The only information that I could point to is the information in adults where it was the methylphenidate versus placebo study, but really that's it. It's very limited and I know we do get asked this question a lot and, you know, without going outside of our directive, you know, what we're focusing on in the report we weren't able to find anything.

Vyn Reese: This is Dr. Reese. There's that one small study with methylphenidate and substance abuse disorder and it shows that it is effective. I mean methylphenidate is not a drug that is commonly abused. I mean it looks like we have some evidence that that's effective. Is that right?

Marian McDonagh: Yes.

Angelo Ballasiotes: Angelo Ballasiotes. Yes, it is effective, but down the road it does lead to problems of abuse. I don't know how big that study was.

Marian McDonagh: It was pretty small and short. I would agree, it doesn't tell us anything about the long-term effect.

Vyn Reese: Well there have been studies with methylphenidate showing it's not a drug that's commonly abused as we know it. I mean it's not a drug like the amphetamines as far as I'm aware.

Bob Bray: This is Bob Bray. I would be interested in others in what their perception is, but I think there's a significant diversion problem with methylphenidate whether or not the individual who is being prescribed it abuses it in high number I can't say, but I think there is a significant diversion problem with all the stimulants including methylphenidate, in my perspective.

Angelo Ballasiotes: I'll echo that. You have a lot of the children's parents using the medication and diverting it for themselves.

Vyn Reese: That may be because they have ADHD.

Angelo Ballasiotes: That could be true.

Patti Varley: This is Patti Varley's comment on that. Usually it's not the patient that's being prescribed the medication that's abusing it. It's usually another relative or friend of the family. I mean it is an interesting concept. There is some data out too about, in children anyway, the fact that treating them actually may contribute to decreasing the risk for drug and alcohol abuse. So, you know, again the data isn't as good on either end as we'd like, but I would say my experience is it usually isn't the patient being prescribed that's abusing, it's usually someone else.

Dan Lessler: Okay. Any other comments or questions for Marian? Marian, are you able to stay on the phone just a bit more?

Marian McDonagh: Sure.

Dan Lessler: Because we're going to have some stakeholder input here and it's helpful sometimes to have you on as our expert.

Marian McDonagh: Okay.

Dan Lessler: So again I have a list of people that have signed up to speak. Again, I would just ask the people to identify yourself and any affiliation and if you're sponsored and as well please limit your comments to three minutes. The first person is Dr. Nate Bailey.

Nate Bailey: I would like to thank the committee. My name's Nate Bailey. I'm a pharmacist and I'm currently working as a medical science liaison for UCB, the manufacturers of Metadate-CD and I'm here to speak to you all on Metadate-CD. Metadate-CD is a schedule two controlled substance used in the treatment of attention deficit disorder and hyperactivity disorder. Metadate-CD…during these three minutes I'd like to highlight some differences between the once daily modified release methylphenidate compounds and primarily I'd first like to say that Metadate-CD was developed as a once daily methylphenidate modified release product to mimic twice daily dosing of immediate release methylphenidate. The conceptual basis behind this design was to put an immediate portion in addition to an extended release portion so we get quick blood levels and we get lasting efficacy throughout the day to avoid that mid day dose of immediate release methylphenidate. Each Metadate-CD capsule contains both immediate release and extended release beads such that 30% of the dose is immediate release and 70% of the dose is extended release. The way that we came by this is the company looked at some other ratios. They looked at this 30/70 ratio, they looked at a 40/60 ratio and they also looked at a 20/80 ratio. Looking at these ratios of methylphenidate extended release and immediate release in patients with ADHD it was found that the 30/70 ratio had a better efficacy in addition to affording a better side effect profile and that's why that ratio of 30/70 was selected.

In addition to that, Metadate-CD is currently available is six dosage strengths. Doses of 10 mg all the way up to 60 mg. These doses can be either in small capsules for easy swallowing, they can be opened and the contents may be sprinkled on a tablespoon of applesauce to further facilitate the administration.

As was mentioned in the slide show that we just looked through there's a recent study with the acronym Comacs that was…Metadate-CD was looked at versus Concerta in an analog classroom setting. This was a double-blind three-way crossover placebo-controlled trial that looked at Metadate-CD and Concerta and placebo in a group of adolescent's ages 6 to 12. What was found according to the Scamp deed department scale that Metadate-CD within the first six hours of the day showed better, statistically significantly better improvement scores when compared to Concerta and placebo. It was also mentioned that both of these products were superior to placebo throughout the whole day.

Finally, adverse event profile with Metadate-CD is typically…parallels that of other stimulant medications. We have in three pooled clinical trials the most common adverse events were appetite loss, abdominal pain, insomnia and pain. And finally in summary, Metadate-CD is a once daily methylphenidate product designed to replace twice daily dosing of immediate release methylphenidate. As such it provides a well tolerated stimulant profile with efficacy both in the morning and in the afternoon and this way we can avoid that mid-day dose on the immediate release methylphenidate. Once again it is available in six product strengths and it is the only one that is available in those six and it also has that optimized ratio to 30/70% immediate release to extended methylphenidate. With that I'd be happy to take any questions if there are any?

Dan Lessler: Thanks. Any questions? No? Thank you.

Nate Bailey: Thank you.

Jim Goddard: My name is Jim Goddard. I'm the director of government affairs for Shire US and we market both Adderall XR and Daytrana. Daytrana is a methylphenidate transdermal system that was approved in April of this year and we started marketing it in June. My request is even though OHSU did not include it in their list of drugs that they reviewed that you do consider it for inclusion on your PDL.

Dan Lessler: Thank you. Any questions? No? Okay. Next is Dr. Ted Dandelkorn.

Ted Dandelkorn: My name is Ted Dandelkorn. I have a clinic exclusive to treating ADHD individuals, adults and children. I've been doing this for about 30 years and we have slightly over 1,000 families that we're following in our clinic and we have a lot of experience with the diagnosis and treatment. It's always fun to come to these meetings on an annual basis to see what kind of progress we've made. There are so many things I could say and I can't take up too much time, but I'm so distressed by some of the studies that are shown. These are all studies that are based on inadequate diagnostic criteria, the DSM3, the DSM3R when we used to look at this as a little boy problem diagnosed with behavioral issues in school. We've come a long way from that and we still put these studies up as though they mean something. It's very frustrating.

We are now doing much more adequate studies with girls, with boys, some of whom are hyperactive, many of them are not. We're now doing studies on adults and even more importantly the criteria for diagnosis is much more appropriate as we're looking at not failure. You realize that we treat these kids…we used to diagnose these kids only if they separated themselves from the peer group. If we did that with any other medical illness you'd have to have a heart attack before we treated your blood pressure. It's bizarre. And we have to get out of this concept that these people have to be bad enough before we treat them, which is what we've always thought about and if they're not bad enough we're not going to do it and we're only going to treat them in school. So it's been very frustrating to watch this slowly develop. Meanwhile I'm taking care of these people and watching them do very well under the right care and guidance for many, many years.

They are only now starting to do studies where they optimize the treatment before they ever look at them. We used to treat these people by putting them on so much medicine per pound—bizarre. It's like I'm going to give you the thickness of their glasses depending on how much you weigh. And then we would pay attention to those studies. And these are the studies we're looking at. People that were treated by medicine whether it be amphetamines or methylphenidate and they were treated by the amount of medicine per pound and they mean nothing. So we're now optimizing, we're actually putting them on whatever medicine we're studying and we're optimizing it to the best dose, the best that we can do and then we're studying them. So we're finally getting to do this more adequately.

We now know that this is a medical condition, a biochemical medical condition, has something to do with the neurotransmitters in the brain, some evidence that it may have to do with the dopamine transporter system, which seems to be working improperly. And as we all know most of the medicines we're using at least either significantly to the most part or at least to some part dopamine reuptake inhibitors. The medicines we're studying are dopamine reuptake inhibitors. And when we use these medicines it makes a significant difference to the way these people perform and function with the normal brain. They don't need therapy, they don't need guidance, they just start functioning better—similar to putting glasses on. If it's a medical condition and if in fact these people have been documented to have this medical condition it doesn't go away when you're 13, it doesn't go away at 4:00 in the afternoon, it is persistent and we've done all kinds of studies to show what happens to these people if we don't treat them—unwanted pregnancies, traffic accidents, failure to be promoted, the marriages that fail, school performance failure, all kinds of failure if we do not help these people function in a better manner and give them success. And since it was initially a behavioral problem we only…

Dan Lessler: Dr. Dandelkorn, I'm going to have to ask you to wind up your comments.

Ted Dandelkorn: Yeah, I will get on with it. My point I'm trying to make is this is a medical condition that should be treated from the beginning of the day to the end of the day and when people get up and start saying

to me they want to [inaudible] medicine that works until 4:00 in the afternoon or they need twice-a-day dosing that's like treating a diabetic with short-acting insulin. We have slowly…the market place has slowly worked towards longer acting, more effective, more therapeutic medicines for the entire day. So I continue to push for medications that work all day from the moment you get up until the moment you go to bed. And we have a few of those on the market.

Dan Lessler: Dr. Dandelkorn, I thank you for your comments.

Ted Dandelkorn: Okay. That's as far as I can go?

Dan Lessler: Yeah. Thanks. Next is Dr. Jeff Hille.

Jeff Hille: Good morning. My name is Jeff Hille and I'm a representative from the medical division of Eli Lilly and Company and I'd like to provide comment in support of maintaining the availability of Strattera for Medicaid patients here in Washington. I'd like to make a few brief points. The first point is that when you look at patients with ADHD not all patients are the same. Comorbidities are common in these patients with up to 65% of patients having at least one comorbidity. When you look at the medications that are available to treat ADHD not all medications are the same. One size does not fit all in the treatment of this disorder. Not all patients respond the same and not all medications may be appropriate for patients based on their comorbid medical profiles. These factors are important to consider when making treatment decisions and when making decisions about the availability of medications for treating this disorder.

Strattera is unique in that it is the only non-stimulant medication with an approval for the treatment of ADHD and as such it represents an important therapeutic option for patients with this disorder. For example, comorbid tic disorders are present in up to 11% of ADHD patients. Stimulant medications are contraindicated or have precautions against use in patients with this comorbidity. Strattera is not contraindicated in these patients and has been shown to be safe and effective in patients with ADHD and comorbid tics. Comorbid anxiety disorders are present in 25% to 50% of ADHD patients. Again, stimulant medications are contraindicated or have warnings against use in patients with agitative states and anxiety. Strattera does not carry this contraindication and has been shown to be safe and effective in patients with ADHD and comorbid anxiety disorders.

Thirdly, comorbid substance use disorders are present in up to 20% of ADHD patients. As members of this committee have previously discussed, some clinicians may be reluctant to prescribe stimulants because of their potential for abuse, misuse and diversion. Stimulants are controlled substances and should be used cautiously in patients with a history of alcohol or substance abuse. Strattera is not a controlled substance and has been proven to lack abuse liability. For these reasons Strattera is not likely to be abused, misused or diverted and may be preferred in patients with a history of alcohol or drug abuse or those residing in a substance abusing environment.

In conclusion, there are a number of important treatment factors to consider when making decisions about the availability of ADHD medications. These factors support the need for a broad availability of medications for the treatment of this disorder including the availability of Strattera. Thank you for your time.

Dan Lessler: Thank you. Any questions?

Patti Varley: This is Patti Varley. I'm wondering if the Oregon people did any review this last time on the liver side effects with Strattera?

Marian McDonagh: Well, you know, the report does comment on it, but we didn't do…there's no comparative evidence. So it's a little difficult for us to pursue that within the constraints of the report itself other than simply pointing people to the evidence on Strattera, you know, the FDA evidence for example.

Dan Lessler: Okay. Thank you. Next is Dr. Patric Darby.

Patric Darby: Good morning. My name is Dr. Patric Darby. I'm a child psychiatrist in private practice just a couple of miles up the road from here. I'm here to speak on behalf of Focalin-XR. I have been a

paid speaker for several different companies in the past, but I am not being compensated in any way for being here today. I just want to let you know that I've been so impressed with this medication since it came out that it's made an outstanding change in my patient's life and their lifestyle. My prescribing patterns remain consistent and they always have, but with the advent of Focalin-XR I give my patients three different stimulants, long-acting stimulant medications to try. I do not create any bias by just suggesting which one they try, but I do give them the mixed amphetamine salts, I give them a long-acting methylphenidate, and I give Focalin-XR. The majority of patients come back to me and tell me they like Focalin-XR best of the three.

In addition, this Focalin-XR is the new single isomer technology, which means that there is a right hand and left hand compound in most medications, or many medications, including many of the medications you're familiar with including sleeping medications, gastric reflux disease, antidepressants and antibiotics. It appears that when you remove that other unnecessary shall we say isomer the medication is a little bit cleaner, more effective and people report to me they have fewer side effects.

Focalin-XR is the only Dexmethylphenidate product on the market today. It seems to be very well tolerated with minimal side effects and although in clinical studies indicate there is no changes in weight or vital signs, my patients subjectively report to me they have better appetites than they did when they tried the other medications. They were not so anxious or irritable and they felt better. Studies by Silva also indicated an onset of action within 30 to 60 minutes.

Many of my patients said they had a slightly longer duration of action and there were clinical studies that stated that using the scamp and the [inaudible] performance test also showed duration of up to 12 hours. Parents inform me of tremendous improvement in their children both in school and at home.

Note: all of these are subjective findings for me, but this is what clinical practice is all about. It's about what parents report and kids report back to me on how these medications work. Also when I see a newly diagnosed child with ADD I often ask the parent, "Who does this kid remind you of most?" Because I met you one of those parents also has ADD. Okay? And Focalin-XR has an indication for treating ADD in adults.

One thing interesting I note is that with this medication insurance companies used to deny this medication until I showed them it was on the DSHS preferred drug list. Once they did that the insurance companies covered it and this I've got to commend that DSHS finally became a leader in treatment medication and I have insurance companies not turning me down anymore because of this. This has been an excellent medication for my patients and that's really what it's all about is patient care. Thank you.

Dan Lessler: Thank you. Any questions? And finally Joe Schwab, Mr. Joe Schwab.

Joe Schwab: In the interest of time my points have already been reiterated by previous testimony. I'll pass.

Dan Lessler: Okay. Thank you. All right. Any last questions for Marian here?

Woman: [inaudible]

Dan Lessler: That's fine. Why don't you come up?

Jennifer Vankowitz: My name is Jennifer Vankowitz, Concerta and McNeil Pediatrics and I'm a medical science liaison and pharmacist. Just a quick couple point. Concerta is unique compared to other stimulant medications. It's once-a-day dosing, 12-hours duration and provides full day coverage into the evening and a couple of particular points I feel are definitely special are that compared…the methylphenidate contained in our tablet is very difficult to extract. It's contained in a polymer and it's in a hard shell and even if you crush it it's very difficult to get the same amount of absorption from the [inaudible]. The compromise of this formulation makes ours particularly very undesirable for abuse.

There was a recent groundbreaking study by Spencer and colleagues back in March looking at pet scans and what they found is Concerta was associated with a longer time to maximum concentration, as well as minimal detection likeability compared to immediate release methylphenidate. And Dr. Norvil [inaudible] wrote an editor supporting this pivotal research stating that it provides evidence that when comparing all oral forms of stimulants you have to keep in mind the way that they are metabolized and that ones that have slower rates of release will be less reinforcing than those with faster rates of release.

Some other quick points. We know that greater adherence to stimulants associated with reduced risk of injury in ADHD children and adolescents. There is data supporting Concerta has greater adherence compared to Metadate CD and Ritalin LA, fewer switches compared to immediate release methylphenidate. There is Texas Medicaid prescription claims database showing that we also have significantly greater rates of persistency compared to Adderall XR and immediate release methylphenidate. Also there's data supporting reduced risk of accidents and injuries in ADHD children and there was three driving studies performed by Cox and his colleagues that showed there were significant improvements in driving scores and driving performance compared to…I'm sorry, on simulated and on road settings. There's also a much more recent study looking at Concerta compared to Adderall XR and it was associated with better driving performance compared to Adderall XR. That's about it.

We know that in summary that untreated ADHD as you've all said has significant costs to our society, healthcare system, patients. Our technology truly less desirable for abuse. It's much harder to abuse it and…I'm sorry, we also have positive data supporting injury outcomes and treatment comes—costs and switching patterns and inherence. Thank you.

Dan Lessler: Thank you. Any questions?

Jennifer Vankowitz: Some of that data is not in the guidelines I don't believe, the Cox studies, the new Spencer article. I don't believe those were included in the most recent update, but those are, I think, important studies looking at adolescents and abusability.

Dan Lessler: Thank you. Marian, are you still there?

Marian McDonagh: I am.

Dan Lessler: I don't know whether…are there any questions for…Alvin?

Alvin Goo: Hi, Marian, it's Alvin again. One last question on Atomoxetine. Were there any studies in patients with substance abuse history?

Marian McDonagh: You know there were none that separated them out. If they were in populations they weren't separated out.

Alvin Goo: But not identified?

Marian McDonagh: Yeah.

Alvin Goo: Okay. Thanks.

Patti Varley: This is Patti Varley. When's the next review?

Marian McDonagh: The date of the next review?

Patti Varley: Uh huh.

Marian McDonagh: That's a good question. It probably…we're working on it so it should be starting in the next month or two.

Patti Varley: So will the new Daytrana patch be included in that database?

Marian McDonagh: Yes, it will.

Patti Varley: And is there a way to focus a little more on the side effect profile of Strattera?

Marian McDonagh: Yeah. You know, I think it's a really good idea that any of you…you've brought up really good issues today and if you suggest those to Jeff Graham to bring to the group for modifying the key questions then we could answer those questions within the review as best we can if we modify the way the questions are stated.

Vyn Reese: This is Dr. Reese. I think that's very important. I think that we need to add safety as issues and observational studies especially in classes of drugs. It doesn't have to be comparative data, but if one drug stands out as having a problem or a class has a problem we need to really highlight those areas so we have better information. I feel like we're not really getting complete studies to look at safety. It's a concern of mine.

Dan Lessler: Okay. Thank you. Marian, thank you very much for your time. We can let you…

Jeff Graham: Let me ask a question. Marian, this is Jeff, are you doing the PPI presentation?

Marian McDonagh: No, that will be Susan Carson and she's ready to go any time.

Jeff Graham: Okay because we may be…we don't know yet, but I'll give a call to you.

Marian McDonagh: All right. Thank you.

Dan Lessler: So actually I think probably the best thing to do here is to turn to the prior motion or motions that we considered and improved here and just to remind people we sort of broke this into two motions—one with the stimulants and the other with Atomoxetine. And actually since…what I might do is turn to Patti and Angelo since I know the two of you were sort of crafted and were very involved in this discussion and maybe we could begin with your comments in terms of whether you think there is need for change and so forth.

Patti Varley: This is Patti Varley and as far as I'm concerned the way they stand based on the data I presented I wouldn't change necessarily anything.

Dan Lessler: Angelo?

Angelo Ballasiotes: I agree with that, Patti.

Dan Lessler: So I'm wondering if there are any other comments. I can't remember the second motion in particular there. There was a minority opinion. I don't know if anybody would want to speak to that with respect to the prior Strattera decision. Alvin?

Alvin Goo: I would just like to ask that we look into other studies comparing non-stimulants and include that in the next review.

Patti Varley: Alvin, I would like that too. I think we addressed it the way we did last time because of the circumstances, but if there was a way to look at that more directly with good data and evidence that would be useful I think.

Alvin Goo: Yeah, if we could just compare the non-stimulants to each other I think that would be helpful.

Dan Lessler: To the extent that there is data to…Jeff, is that…can we request that of…?

Jeff Graham: Yes. We have to remember there are 15 other participating organizations in this process now. So they would have to agree with that, too. I think what happened was this got to be such a huge study that it was going to give us…people felt they certainly weren't going to get the information they wanted, but I will bring it up.

Dan Lessler: Thanks.

Patti Varley: Thanks.

Dan Lessler: Are there any other comments on either of the previous motions? Or are there other observations or comments that people think are relevant in terms of anything new that might have been presented today? Would it be reasonable then to again break these motions out into two motions and begin with the stimulants? Is there somebody who would be willing to put forward a motion even if it's the same as the previous motion?

Patti Varley: Yes. This is Patti Varley. I'll be happy to put forward this motion again. After considering the evidence of safety, efficacy and special populations for the treatment of ADHD…and I would say again maybe just to be consistent that we spell it out with the acronym. I move that methylphenidate based and amphetamine based agents of both long and short acting formulations are safe and efficacious. A long and short acting formulation of each stimulant should be preferred drugs on the Washington State Preferred Drug List. No single stimulant medication is associated with fewer adverse events in special populations. The stimulants listed above shall not be subject to therapeutic interchange on the Washington Preferred Drug List.

Dan Lessler: Okay. Is there a second?

Jason Iltz: I'll second it again. This is Jason.

Dan Lessler: Okay. All those in favor, I.

Group: I.

Dan Lessler: Opposed, same sign. Okay. I just hope this doesn't mean we're reminiscent of just a few days ago. Um, okay. So next if we could consider Atomoxetine and again I'm wondering if there is a motion?

Patti Varley: This is Patti Varley. I'm happy to repeat the motion from last time. After considering the evidence of safety, efficacy and special populations for the treatment of ADHD, I move that the non-stimulant Atomoxetine is efficacious and should be included as a preferred drug on the Washington State Preferred Drug List.

Dan Lessler: Is there a second?

Woman: [inaudible]

Dan Lessler: Right. I think there was a feeling that we just didn't have enough data particularly with respect to the potential liver toxicity. Patti, did you want to comment on that?

Patti Varley: This is Patti Varley again and I…that's why I keep raising the question. I have not seen further evidence one way or the other and I would like to see it. I'm still concerned about it being there and maybe it's because I've been around too long and Pemoline was one of those things that…

Dan Lessler: So is there a second?

Man: I'll second it.

Dan Lessler: Okay. The motion has been seconded. Any further comment or discussion? All those in favor say, I.

Group: I.

Dan Lessler: Oppose, same sign.

Alvin Goo: I.

Dan Lessler: Okay. Did you get that? Okay. So the motion passes and I think we're done with this class and can move on to the PPIs here.

Jeff Graham: Susan will be any minute calling in now.

Jason Iltz: Dan, can I make just one comment before we leave this group?

Dan Lessler: Sure.

Jason Iltz: This is kind of going back to…this is Jason. This is kind of going back to Alvin's comment earlier and the question I ask is, "How is this now going to be listed in the actual PDL?" I understand Alvin's point a little more clearly now when I see how it was published the last time. What it showed was all of the different medications that were, in my mind, looked to have been considered for treatment of this particular disorder and then there was preferred drugs that were included. If you look at the list there were things like Bupropion on there and I think to a practitioner they might assume that maybe it's not covered for that indication or something. So now is the list going to be shorter or is there going to be a statement made that says, you know, drugs outside of this specific class may also be useful or something? I don't know if everyone is looking at the way it is listed in the P&T, but I see why it was brought up in terms of confusion as to what really could be used or could be covered.

Jeff Graham: This is Jeff. Why don't you let us mull that over and see what we might be able to do because I don't think we can make a decision here, right now.

Jason Iltz: Right.

Jeff Graham: But I think…Susan, did you come on?

Susan Carson: Yes, it's me.

Jeff Graham: Okay.

Carol Cordy: This is Carol Cordy. I'm just covering for a minute. Why don't you go ahead? Do we have the PowerPoint up? Okay. Susan, we have the PowerPoint up if you want to go ahead.

Susan Carson: Okay. Great. Thanks. Okay. So the first slide shows that this is the fourth update of the PPIs report. If you go to slide number 2 included populations…we actually had two changes to the scope of the report for this update. One was that children were added on the included population and also we added non-erosive GERD. Previously we only had erosive esophagitis as an included population.

Jeff Graham: Susan, this is Jeff Graham. Can you speak up just a little bit?

Susan Carson: Sure.

Jeff Graham: Thank you. That's much better.

Susan Carson: Okay. So we added children and then also non-erosive GERD as our included populations this update.

Slide number 3 shows our included drugs, the five PPIs and we added no new drugs this update.

Slide 4 shows our included outcomes: symptoms, endoscopic healing, eradication rates, functional outcomes, qualify of life and adverse effects and these stayed the same for this update. We had no changes.

Next slide. So I'll focus only on the new evidence since this is an update. So for erosive esophagitis there was one new fair quality head-to-head study that we added, Chen 2005. And this

study compared healing rates at eight weeks with esomeprazole 40 mg versus omeprazole 20 mg. And the healing rate at eight weeks was 64% for esomeprazole and 45.5% for omeprazole. This rate was lower than in most of the other studies with the same comparators. And they didn't look at healing at four weeks in this study. So adding this study to our existing meta-analyses the pooled risk difference between esomeprazole 40 and omeprazole 20 was slightly increased to 6%, but the study does not change our existing conclusions, which were already that esomeprazole 40 mg had a higher healing rate at eight weeks than omeprazole 20 mg. So it's consistent with other evidence.

Next slide. New evidence for non-erosive esophagitis. This is our new population this update. So there were three head-to-head studies in patients with endoscopy-negative GERD. All of these included esomeprazole 20 mg compared to another PPI, but the outcomes were different in these three studies. The outcomes were complete resolution of heartburn in one study, time to release in another, and time to first 24-hours without symptoms in the third study. And then comparing esomeprazole to omeprazole, pantoprazole and rabeprazole in the three studies. They all found no differences between the PPIs.

Next slide. This is a table that summarizes the indirect evidence for the outcomes at four weeks in patients with non-erosive GERD. It's either endoscopy negative or empirically treated GERD. So ENRD stands for empirically…sorry, it stands for endoscopy negative reflux disease. And then the table shows the ranges for heartburn relief and other symptoms that were found in these studies. These data come from a Cochran systematic review that was conducted in 2004 and we also added more recent studies that weren't included in that review because they hadn't been published at the time. So you can see from the table that in some individual studies the rates of heartburn resolution or resolution of symptoms…of other symptoms were higher than in others, but overall the rates were similar and we really can't conclude that one PPI is superior to another from this body of evidence. One reason is that for drugs other than esomeprazole and omeprazole the evidence comes from only one study. The number of studies is shown in the first column. And also this evidence is indirect. They are not head-to-head studies. It's indirect evidence from placebo or active control trials.

Next slide, slide 8. Prevention of relapse. There were no new head-to-head studies that compared PPIs for prevention of relapse of erosive esophagitis for this update. We added two new fair quality trials. One compared rabeprazole versus placebo and another compared pantoprazole versus ranitidine. The new studies don't add comparative evidence and their results don't change our previous conclusions. Just to summarize our previous conclusions were that there was good evidence that there is no comparative difference between omeprazole, lansoprazole and rabeprazole for this outcome. That comes from head-to-head evidence. And then there's also evidence from two six-month studies that relapse rates were lower for esomeprazole 20 mg compared with lansoprazole 15 mg or pantoprazole 20 mg.

Next slide. This is prevention of relapse in non-erosive esophagitis, again, our new population. We included one fair quality head-to-head trial of prevention of relapse in non-erosive esophagitis. This was an open label study that compared esomeprazole 20 mg on demand to lansoprazole 15 mg given continuously for six months. So one drug was given on demand, the other was given continuously. So they're not really directly comparable. In this study more patients on lansoprazole discontinued, but the discontinuations due to heartburn were not significantly different between groups. Additionally, we included two placebo-controlled trials of on-demand rabeprazole 10 mg and esomeprazole 10 mg. And also a placebo-controlled trial of continuous omeprazole, which isn't on this slide. All of these studies found fewer discontinuations due to heartburn with the active comparator than with the PPI at six months.

Next slide. Esophagitis in children. We identified no head-to-head trials in this population. We did include one fair quality placebo-controlled cross over trial of omeprazole 10 mg to 20 mg per day in 30 infants age 3 to 12 months and they had GERD defined either through endoscopy or through a reflux index, which was defined as the percentage of the total recording time of pH less than four…more than 5% of the time. And in this study after two weeks there was no difference in infant cry or fuss time or scores or parent assessment or infant irritability between placebo and omeprazole. The reflux index did decrease with omeprazole, however. And also a poor quality trial of omeprazole compared to high dose ranitidine in children with reflux that was refractory to

standard dose ranitidine found both drugs were effective, but we called this poor quality because there was a high drop out rate, it was 19% and they did not do an intention to treat analysis. So the results of the study are not reliable.

Next slide. We're on slide 11. Reporting of adverse events in children was limited to short-term trials and one open label uncontrolled study with a mean follow up of 12 months. In the short-term trials, which included children taking omeprazole and rabeprazole there was no serious adverse events reported. In the uncontrolled study of omeprazole for esophageal reflux in 15 children, 47% had elevations of liver enzymes and 74% had hypergastrinemia. And then in a 28-day before and after study of pantoprazole for reflux in 18 children, one child had elevated liver enzymes and 28% had hypergastrinemia.

Next slide. Let's move on to our new evidence for ulcer. For gastric ulcer a fair quality, head-to-head trial found no difference in eradication rates between omeprazole and rabeprazole. And then there's no new evidence for duodenal ulcer. A post-hoc subgroup analysis of a trial with patients taking NSAIDs and low dose aspirin found no differences between misoprostol, lansoprazole 15 mg and lansoprazole 30 mg at 12 weeks. All of the active treatments were more effective than placebo.

Next slide. We added three new studies of H-pylori eradication in adults. They all found no differences between lansoprazole versus omeprazole, which were used in various combination regiments. And in children two fair quality placebo-controlled trials found no additional benefit of adding lansoprazole to antibiotic therapy alone.

Next slide. Key question 4 addressed comparative evidence in subgroups based on demographics or other factors. One study found higher H-pylori eradication rates in patients older than age 50 compared to those who were younger, but comparisons among the PPIs were not made in this study. So we can't…it doesn't give us evidence about comparative effectiveness. And a small study found no difference in ulcer healing rate between rabeprazole and omeprazole by genotype. In a child omeprazole in Japanese patients who had recurrent esophagitis found no differences in efficacy or safety by genotype.

Next slide, slide 15. We found new evidence from a perspective cohort study in over 400 pregnant women who had sought counseling after exposure to PPIs during pregnancy. Most of them had taken omeprazole, 295 of the 410 had taken omeprazole. And there were no differences in the rate of major anomalies between each of the three groups. The three groups were patients taking omeprazole, lansoprazole or pantoprazole. So there was no difference in anomalies between each of the three groups compared to the control group of women who hadn't taken a PPI. This slide show the relative risks in each group. There was a reduction of 60 grams in median birth weight in omeprazole exposed versus control groups, but no differences in median gestational age of delivery, rate of pre-term birth, rate of miscarriages, ectopic pregnancies or stillbirths in exposed versus control groups. The study found there was a higher rate of elective terminations of pregnancy in the omeprazole and lansoprazole groups compared with the control group of women who didn't take PPIs. In two women in the omeprazole group, one in the lansoprazole group, zero in the pantoprazole group, and five in the control group, the reason for termination was because of a prenatal diagnosis of anomaly.

Next slide. This is the last slide and it just summarizes the new evidence for update number 4. For erosive esophagitis new evidence does not change conclusions. For non-erosive esophagitis we did not find differences in symptom resolution between PPIs. For ulcer and H-pylori new evidence also does not change our current conclusions. In children the evidence is too limited to make any conclusion about comparisons among the PPIs. And for subgroups new evidence supports previous evidence regarding a lack of a difference between PPIs based on genotype and new evidence on exposure to PPIs during pregnancy does not support clear differences between PPIs and risk of malformation. And that concludes the presentation.

Dan Lessler: Great. Thank you very much.

Susan Carson: You're welcome.

Dan Lessler: And I was going to open it up here, Susan, if you have a moment to see if there are questions for you from P&T committee members.

Patti Varley: This is Patti Varley. My question about children is the data says there's no good evidence about comparison data, but is there any evidence about children being more sensitive in general to the side effect profiles?

Susan Carson: Then adults?

Patti Varley: Yes.

Susan Carson: No. We didn't find…we found very limited evidence. We didn't find any comparative evidence like that and the evidence just in general for adverse events in children was…it was such a small body of evidence really just from very short-term trials and a couple of uncontrolled studies.

Patti Varley: Yeah, I was just struck by the liver results myself.

Susan Carson: Yeah.

Dan Lessler: Other questions from…okay, Susan, can you stay on the line maybe just another ten minutes or so? We have some stakeholder input and it can be helpful sometimes to have you available for questions. First is Mr. Philip Olufson.

Philip Olufson: Hi. I'm Philip Olufson representing Wyeth and I just want to make a few quick points to consider in your decision. First of all Protonix, pantoprazole 40 mg has two studies in night time GERD over one year with over 100 patients each. They show greater than 90% nights heartburn free. Representing the true 24-hour control. Secondly, previously reviewed by this committee I believe the Gilluson(?) in 2004 pantoprazole 40 showed equivalent to esomeprazole 40 mg in healing of esophageal lesions in relieving GERD related symptoms and then thirdly food affect. Pantoprazole 40 when given with food delays the area under the curve and absorption by two hours, but it does not alter the area under the curve, which is not the case with some of the other PPIs. It may lead to consideration with compliance issues in patients. Thank you.

Dan Lessler: Thank you. Any questions? No? Okay. Next is Dr. Lein. Am I saying that right?

Diana Orentas Lein: Hi. My name is Diana Orentas Lein and I am a scientific affairs liaison for Santarus and I want to thank you for the opportunity to present data on Santarus' product, Zegerid, which is an immediate release formulation of omeprazole and it's available in both a capsule and a powder for oral suspension formulation.

All PPIs are acid labile and for that reason all of the other orally administered PPIs delay the release of the PPI using an enteric coating to protect the drug from degradation by gastric acidity. In contrast Zegerid neutralizes gastric acidity using an antacid buffer, which is administered in combination with a PPI micronized omeprazole. This combination of the micronized omeprazole together with sodium bicarbonate leads to rapid neutralization of the gastric acidity. It protects the pro drug, but it also allows for the rapid absorption of the drug so that you have peak plasma levels within 30 minutes. The FDA in reviewing this data has classified Zegerid as the only immediate release PPI and for that reason it is not considered AB rated with any of the other omeprazole products.

These pharmacokinetic differences do translate into pharmacodynamic superior control. In Santarus' pharmacodynamic trials 40 mg of Zegerid when administered once a day yield an 18.6-hour pH control over 4. In a hospital study published in the Journal of Critical Care Medicine 40 mg of Zegerid administered through an NG tube to critically ill patients raised the effective pH over 4 in the majority of patients. In fact, on all 14 days of the trial the average pH was greater than 6 in the Zegerid arm. So this, again, speaks to its effectiveness as well as the convenience of administration through an NG tube for the powder for oral suspension formulation.

And finally, in the outpatient setting Zegerid has demonstrated superior pH control at night when administered prior to bedtime in patients with nighttime heartburn. In studies published by both Don Castell and Philip Katz Zegerid administered prior to bedtime demonstrated superior pH control, the integrated gastric acidity, which is the accumulative amount of acid produced over the nighttime hours was five times lower in the Zegerid arm than in the esomeprazole arm and 7 times lower in the Zegerid arm than the lansoprazole arm. In addition, the nighttime dosing prior to bedtime is different from the ACG (American College of Gastro Oncology Guidelines), which recommend enteric coated PPIs be taken prior to dinner in nighttime dosing. So this is a benefit to the non-compliant patient.

In conclusion, in previous there's been some discussion about the need for a liquid formulation by this committee and we feel that the powder oral suspension would meet that need especially in patients that have difficulty swallowing, patients with an NG tube and patients with dysphasia. In terms of the NG tube use, in vitro studies have demonstrated that down to a [inaudible] of 8 there is no significant loss of material and in our hospital study there was no clotting of the tubes or any difficult with the NG tubes with the administration of Zegerid. Any questions?

Dan Lessler: Any questions from [end of Side A]

[Side B]

Julie Baker: My name is Julie Baker and I'm a PharmD with Tap Pharmaceuticals. Thank you for offering me the opportunity to speak with you today. I really appreciate the drug review of the PPI class that's been assembled and I've reviewed it and as a pharmacist I do agree with your conclusions and given that I'm not going to talk about safety and efficacy for lansoprazole or the brand name Prevacid, but I will talk about some of the benefits that Prevacid offers that are unique and that have gained it a position on the Washington PDL for this year.

Prevacid is the only PPI that is approved for use in children from the ages of 12 months of age to 17 years of age and that is for the indications of symptomatic GERD as well as erosive esophagitis. It's very convenient to dose for children 1 to 11, it's based upon their weight and for children 12 to 17 it's based upon their diagnosis. In addition to having the indication for pediatrics there are many dosing options available. That is another benefit that Prevacid offers. Of course you're familiar with the Prevacid capsule, which can be taken, of course, intact, but also sprinkled onto soft food or administered with a quarter-cut of juice. And if patients do not find that that works for them there's of course the Prevacid packet for oral suspension, which can be mixed with two tablespoons of water and it's strawberry flavored and very pleasant for children or anyone who has trouble swallowing a capsule to take. If neither the capsule or the Prevacid packet for oral suspension work for patients then there is the Prevacid SoluTab, and that is of course equivalent to that capsule. It is absorbed the very same was as the capsule. It's absorbed in the duodenum and it's just comprised of much smaller micro granules of lansoprazole than the capsule contains. What that means is that if it is placed on the tongue and allowed to dissolve there it breaks down into these micro granules that are also enterically coated so it can't be chewed or crushed, but those micro granules are much easier to swallow by children or any patient who was dysphasia or any esophageal stricture. Additionally, it can be administered via an oral syringe, which is a really good option for caregivers of small children who are difficult to dose. A two-year-old can easily be administered a Prevacid SoluTab with 5 ml or 10 ml of water in an oral syringe and they can then get the full dose and be assured that there's no struggle involved with the administration. I didn't mention yet, but it is strawberry flavored like the oral suspension is so that's also something that makes it pleasant for children.

In addition to oral syringe administration Prevacid SoluTab is also approved for [inaudible] administration and like Zegerid it does have approval for use in NG tubes as small as 8 French. So

that's another alternative for patients who require NG administration and can't take the product orally.

So in conclusion I just wanted to remind you that Prevacid does offer unique benefits in terms of its pediatric indication all the way from 12 months of age to 17 years of age, as well as the various administration options that can make it the right choice for any patient in the population from 12 months onward. If you have any questions I'd be happy to entertain them at this time, but I'd just like to reiterate that we would respectfully request that Prevacid be maintained on its position for the Washington PDL.

Dan Lessler: Thank you. Any questions or? Thank you. And finally Dr. Stogsdill.

Doug Stogsdill: Thank you. I'm Doug Stogsdill. I'm a regional scientific manager with AstraZeneca and I want to thank you for this opportunity. I'm not going to rehash so much of the data that was presented by the EPC and they did a wonderful job in their review. But one thing we want to remember is that all proton pump inhibitors work the same way by blocking the hydrogen potassium ATPAs. And so by using a surrogate marker of pharmacodynamics of pH control it can be very useful in comparing agents to one another.

In 11 comparative trials esomeprazole was shown to be more effective or shown to have a significantly greater effect in controlling pH and this actually included a five-way cross over where all patients were given all the brand of PPIs and again it showed to be much better. This also translates into clinical effect, which we were presented today by the report stating that they do show a much better or a specifically better healing at eight weeks over all the branded PPIs. But even more importantly are those patients who have more severe disease and in these trials patients who have the more severe disease or the [inaudible] grade Cs and Ds got a much better benefit from the differences between esomeprazole and the other products. One thing we need to remember on that is that in our trials 25% of these patients had more severe disease. So this is a large population of patients and these are the patients that may have more severe disease going on to more types of effects. So it is reasonable that in healing of erosive esophagitis a product that has better healing throughout the grades of severity is a better option.

Now as far as other indications we do have some new indications that were presented. For instance, the continuous use of non-steroidals in patients who are at risk for developing gastric ulcers we now have that indication, as well as the long-term treatment of pathological conditions for instance Zollinger Ellison Syndrome and the short-term treatment of gastroesophageal reflex disease for up to eight weeks in adolescent patients age 12 to 17 years.

We also have some alternative administration options. These would include opening the capsules and sprinkling it on food, mixing it with water, being able to put it down an NG tube, as well as a delayed release oral suspension that can be administered orally or via the NG tube. An IV formulation is also available and is indicated for short-term treatment of patients with gastroesophageal reflex disease.

So to conclude esomeprazole is pharmacodynamically more effective than other PPIs, especially in pH control. Esomeprazole has greater efficacy in healing of erosive esophagitis than omeprazole, lansoprazole and pantoprazole through eight weeks. And has greater efficacy in healing of more severe grades of erosive esophagitis than omeprazole, lansoprazole and pantoprazole in those eight-week studies. We have new indications and esomeprazole also has alternative administration options. Thank you and I will entertain any questions.

Dan Lessler: Thanks. Any questions? No? Thank you. Susan, are you there?

Susan Carson: Yes.

Dan Lessler: Are there any other questions for…? No? I think we're all set. I appreciate your time and we can let you go.

Susan Carson: Okay. Great. Thank you.

Dan Lessler: Bye, bye.

Susan Carson: Bye.

Dan Lessler: So maybe we could just turn to the previous motion and people could take a look at that. I'm wondering if there's anybody who sees any need to make any modification to it.

Vyn Reese: I'm Dr. Reese and it looks like the data is pretty much the same as it was last time. There hasn't been any major discoveries that have changed our previous conclusion. So I think probably the previous motion stands. I can just re-read it because I made the motion last time and Dr. Bray seconded it.

Dan Lessler: Okay. Is there any other comment? Why don't we go ahead and you make that motion. That would be great.

Vyn Reese: Do you want to bring a new template up or just…okay. After considering the evidence of safety, efficacy and special populations, I move that rabeprazole, omeprazole, omeprazole, pantoprazole and esomeprazole are safe, efficacious and have no differences in adverse events in special populations. They can be subject to therapeutic interchange in the Washington Preferred Drug List. A pediatric formulation needs to be included on the Washington Preferred Drug List.

Dan Lessler: Is there a second?

Bob Bray: Second. This is Bob Bray.

Dan Lessler: Any other comment or discussion?

Jason Iltz: This is Jason. My only question would be do we want to add what is a little bit different entity, I guess, and that would be the omeprazole/sodium bicarbonate formulation? Because that was included in this review. Is that good?

Dan Lessler: Yeah. I guess we could specify that.

Jason Iltz: I think we could say add one more med, which would be omeprazole/sodium bicarbonate.

Dan Lessler: Then we would take that as a friendly amendment then? Okay. All right. So with that I think we can go ahead and vote. All those in favor say, I.

Group: I.

Dan Lessler: Opposed, same sign. Okay. The motion passes and we can adjourn until 1:00. Thanks.

I think we're just about to…Janet, yeah. So we can get going. Roger, we've got your first slide, your title slide of your PowerPoint projected here. So you can take it from there. Just tell us when you want to change slides.

Roger Chou: Great.

Dan Lessler: Thanks.

Roger Chou: So I'll be presenting the results of our third update on our drug class review on COX-2 inhibitors and NSAIDs. You can go to the next slide.

Just to remind everybody that a lot of this, the material in the update is based on a report that we did for AHRQ on drugs for osteoarthritis, a comparative effectiveness review and that full report is up on our web site. Our goal when we wrote the update was to really not repeat stuff that was in the AHRQ report, but to kind of summarize things and then to flush out areas that weren't covered in the report, but were of interest to participating members of DERP. So just a reminder. The search strategy is a typical search strategy, looking at electronic databases, soliciting pharmaceutical companies for submissions and looking at reference lists. We also looked at the Cochran database of systematic reviews, the Bandolier website, which does a lot of pain related systematic reviews, also the Canadian Agency for Drugs and Technology in Health. It used to be CODA, I believe and changed its name. We no longer used EMBASE. It's incorporated in Cochrane, in part, and then we just don't…it's very costly to use and we don't actually get much out of it so we've actually stopped using EMBASE.

Next slide. For data collection and analysis, again, typical methods. I'm not going to go into them in detail, but we assess studies for inclusion. We rated the quality of studies and abstracted the data and then synthesized the data qualitatively and we allocated grades for the quality of evidence…for the body of evidence for each question using our standard DERP methods.

Next slide. In terms of the key questions there were a few relatively minor changes. One was that we removed direct comparisons of coxibs mainly because the only coxib that's available now in the U.S. or Canada is celecoxib. So there are no head-to-head comparisons between coxibs. The other change we made was that we compared between celecoxib, other NSAIDs and the combination of a nonselective NSAID plus an anti-ulcer medication. We also reorganized the results so that the short-term evidence is distinct from the long-term evidence and also kind of expanded the discussion on use of these drugs in patients on concomitant anticoagulants or aspirin.

Next slide. No changes in the populations reviewed for this report. There are kind of general patients with chronic pain, osteoarthritis, rheumatoid arthritis, etc.

Next slide. In terms of inclusion criteria, in terms of the interventions the main change was we took out rofecoxib and valdecoxib, which again are no longer available. They were voluntarily removed from the market and then we added the Canadian products, tiaprofenic acid and tenoxicam. We also added salsalate, which is related to aspirin.

Next slide. In terms of outcome there were no changes in the outcomes we looked at—pain, functional status, discontinuations due to lack of effectiveness.

Next slide. So an overview of the new evidence we found for this report. Nine new randomized controlled trials, 21 systematic reviews, 32 observational studies of adverse events, and again referring to the AHRQ report that's available on the web, which I think is about 130 pages long or something just as a warning. There is an executive summary that kind of summarizes it as well.

Next slide. So in terms of efficacy results for all NSAIDs we really found no new evidence that contradicted what we found before. There are no clear differences in pain reduction across all of the included drugs in this report. So all NSAIDs appeared roughly similar for pain relief and functional status when that was looked at.

Next slide. So for celecoxib in terms of GE safety…in terms of short-term GI safety the CLASS findings supported…are supported by new evidence. The main new evidence being a 2005 meta-analyses of 18 short-term randomized controlled trials. Short-term meaning generally less than three months. I think all of them were less than six months, but most were, you know, in the eight-week to three-month period. So this meta-analyses found a decreased risk of GI adverse events relative to non-selective NSAIDs during the first six months of therapy. In terms of long-term data there's very little long-term evidence from controlled trials, from randomized controlled trials. Observational studies are actually inconsistent. So some of them show that celecoxib is associated with a lower risk of serious GI events beyond six months. Others don't show any protective effects.

Next slide. In terms of the cardiovascular safety of all of these drugs this is an area that as many of you know is we're getting new studies published almost every week. At the time the report was completed the evidence seemed to show that there is a higher risk of myocardial infarction with celecoxib compared to placebo. The risk ends up being about one additional myocardial infarction for every 300 patient years of exposure. So pretty small risk, but present. A lot of this is based on a large meta-analyses by Kearney et al published in BMJ with a relative risk of 2.1 and significant confidence intervals. There was another smaller meta-analyses that essentially found similar results. It included less trials so it had wider competence levels. Just to note that most of the heart attacks that were observed in the meta-analyses were seen in two large, long-term polyp prevention trials. So the duration was up to three years, 3,600 patients were randomized and used pretty high doses in both trials up to 800 mg daily. Something like 60% of the events were seen in those two trials. So it's unclear actually, there's so few events in trials with lower doses or shorter duration that it's hard to know. I mean statistically you don't really see a difference in terms of estimates of risk, but there are so few events in the short-term trials and the shorter…and the lower dose trials that it's hard to make any reliable conclusion about dose and duration and increased risk. Observational studies, again, found mixed findings if you combine all the studies there's no increased risk, but some studies did find some increased risks and others didn't. So there's some inconsistency there.

Next slide. In terms of other serious adverse events we found no consistent differences between celecoxib and other NSAIDs for mortality, development of hypertension, CHF, edema, renal function, and hepatotoxicity. All of the NSAIDs are associated with these kinds of events and so far no clear differences.

Next slide. Meloxicam, which is considered a partially selective NSAID in terms of safety results for GI safety we found lower…PUB is perforation, ulcer or bleed rates for meloxicam versus nonselective NSAIDs, but these are from earlier and flawed meta-analyses of short-term trials and we actually don't see the same thing in new longer term trials. There's a similar rate of GI hemorrhage for meloxicam and nonselective NSAIDs after six months. In one study and similar GI complication related hospitalization rates from meloxicam and nonselectives after 14 months in another. In terms of cardiovascular safety we only have data from observational studies, which did not show an increased risk from meloxicam, but again that's just observational data and other serious adverse events have not been well studied with meloxicam.

Next slide. Nabumetone and etodolac or other partially selected NSAIDs and evidence remains limited for both of those. For nabumetone a previous meta-analyses found fewer PUBs in treatment-related hospitalizations with nabumetone versus nonselectives after three to six months. This is based on, you know, small numbers of trials and kind of not optimal quality data. There is one new observational study that found a lower risk of all-cause mortality for nabumetone versus nonselectives and again hard to make much of that. It's one observational study and it hasn't been replicated in any other finding. So we don't place a lot of weight on that result. Etodolac – the only evidence comes from new observational studies, which found a similar risk of PUB rates relative to naproxen or nonuse.

Next slide. So far all the other NSAIDs, the nonselective NSAIDs for GI safety all of the NSAIDs appear to be associated with relatively similar risks of serious GI events relative to nonuse. This is from numerous trials and observational studies. There was one new review of randomized controlled trials that found fewer non-serious GI events. So this is things like dyspepsia and non-bleeding ulcers and stuff like that. For tiaprofenic acid versus indomethacin that's based on just a few studies. There aren't a lot of studies of tiaprofenic acid.

Next slide. In terms of cardiovascular safety the…we found all…evidence…some evidence that all nonselective NSAIDs other than naproxen appear to have similar cardiovascular risk profiles when compared to COX-2s, each other, or nonuse. So this is based in part on this big meta-analyses by Kearney et al, 138 trials, the biggest study out there. They went back to all the manufacturers and asked for unpublished cardiovascular safety data for all the nonselective NSAIDs as well as for the selective NSAIDs. Most of the data was for the drugs ibuprofen, diclofenac and naproxen and most of it was for high dose. And naproxen in that study was the only drug that was cardiovascular risk neutral. COX-2s had a higher risk of cardiovascular events than naproxen with a relative risk of 2.04. Confidence intervals were significant and then the risk with the ibuprofen and diclofenac were similar to the COX-2s. A review of 11 observational studies found…was consistent…naproxen was, you know, cardiovascular risk neutral in that study as well and maybe a little bit protective in that study. In other new observational studies naproxen had a neutral cardiovascular effect relative to nonuse. So most of the evidence seems consistent. Now there is one new study just released I believe a couple of weeks ago. So this is the Alzheimer's prevention trial called ADAPT. So this wasn't included in the report. It was published too late, but this was a study that was stopped early by the NIH because it actually found an increased risk of bleeding with naproxen versus either celecoxib…excuse me, an increased risk of myocardial infarction with naproxen versus either celecoxib or ibuprofen, I believe, was the other comparator. There are some problems interpreting that data. One is that it's based on early hazards ratios. So they stopped it based on a hazard ratio that was significant, but hazard ratios are notoriously known to be unstable when there is not too many events. And so those numbers can actually fluctuate quite a bit while the evidence is accumulating. The other problem interpreting those results are that they didn't use any formal stopping rules. So this study was stopped and it's been highly criticized for being stopped in light of the fact that the hazard ratio was used and it may have been too early to really make any judgments about how reliable that data is. The more you look at the…at data on an interim basis the more likely you are to find kind of spurious associations and so…like I said it's been published and released and with a lot of caveats even from the investigators themselves who basically say that they're not sure what to make of that. So that's the one piece where…that shows that naproxen may not be cardiovascular risk neutral, but there is no other studies like that so far.

Next slide. In terms of other serious adverse events really no clear differences between any of the NSAIDs and the new evidence is too limited to draw additional conclusions.

Next slide. So looking at nonselective NSAIDs plus an anti-ulcer medication for GI safety. Misoprostol is the only gastro protective agent, which has been shown to decrease the rate of clinical GI events when taken with an NSAID. That's the MUCOSA trial. The problem with misoprostol is it is very poorly tolerated. So most people can't take the medication. They get nausea and dyspepsia and stuff like that. Misoprostol, H2 blockers and PPIs have all been shown to reduce endoscopic gastric and duodenal ulcers. So not necessarily, you know, clinical bleeds and what not; however, clinically symptomatic ulcers with short-term use and we found no new evidence on this topic.

Next slide. For salsalate if you remember salsalate is kind of the pro drug of acetylsalicylic acid. At one time it was thought to be safer than other NSAIDs in terms of GI risk and at one time was actually one of the recommended medications when somebody needed to be on anticoagulation and required an NSAID as well. We looked back at all the data on salsalate safety and really found that the evidence was too limited to draw strong conclusions about differential safety. Much of the conclusions about, you know, superior safety of salsalate are based on the ARAMIS database studies, which are really kind of flawed observational studies that don't meet current standards for, you know, high quality observational studies. They also use combined outcomes and a lot of them aren't the kind of GI events that we're concerned with meaning bleeds and perforations and things like that. In terms of GI related hospitalizations a single newer observational study found similar rates of GI related hospitalizations with salsalate compared to nonselective NSAIDs after 14 months.

Next slide. Tenoxicam and tiaprofenic acid are the two NSAIDs that are available in Canada. We probably don't need to talk about them here since they're not relevant. So we'll just skip that. There's really not much on either of them.

Next slide. Efficacy and safety in subgroups. In terms of demographics we found…for demographic subgroups we found no new evidence. In the elderly a meta-analyses of celecoxib and naproxen found similar effect on the WOMAC and SF-36 scores; overall incidents of GI adverse events was lower with celecoxib. In terms of gender most studies included a majority of women, but there weren't any clear differences in efficacy or safety based on gender. And then for race or ethnicity really very little data.

Next slide. The other subgroups that we were interested in were persons taking concomitant anticoagulants or aspirin. In terms of concomitant anticoagulation we found inconclusive evidence in two new small observational studies. One found bleeding risk with celecoxib was similar to the nonselectives in one study and the other found a greater bleeding risk with a nonselective compared to partially selective NSAIDs in another. So really no conclusive data from those. For concomitant aspirin use a new review of randomized controlled trials found similar increases in endoscopic ulcer rates for celecoxib and nonselective NSAIDs meaning that the celecoxib didn't seem to lead to better GI safety when people were taking aspirin as well.

Next slide. The other subgroups we were interested in were high-risk patients. In patients with a recent GI bleed there was no clear difference between…in recurrent ulcer bleeding rates in patients receiving celecoxib versus a nonselective NSAID plus a PPI. What should be noted is that in both of those trials the rebleeding rates were really pretty high. They were about 6% in both groups after six months and so, you know, neither comparison really seemed to be particularly safe in really high risk patients for GI bleed. In terms of cardiac/renal comorbidities one new observational study

found lower rates of death and congestive heart failure recurrences for celecoxib relative to nonselectives and again that's a single observational study.

Next slide. So that's the summary of the update and again, like I said, this is a rapidly evolving field and trying to stay on top of it is very difficult, but I tried to highlight most of the new changes and most of the new data. So…

Dan Lessler: That's great, Roger, thank you. I was going to open it up here for committee members to address questions to you. Are there any questions from anybody on the committee at this point? Roger, actually I did have a question about the most recent Alzheimer prevention trial that you brought up.

Roger Chou: Yes.

Dan Lessler: And you mentioned that in that case the risk of MI, I believe, was somewhat higher in the Naprosyn group?

Roger Chou: Yes.

Dan Lessler: Was that Naprosyn compared to celecoxib and ibuprofen or were celecoxib and ibuprofen broken out individually?

Roger Chou: I actually just pulled it. I happen to have it on my desk. So it was celecoxib versus naproxen versus placebo. So sorry, I just [inaudible] there. And it was a higher risk with both…so naproxen was…had a rate of…combined…so they used also a combined outcome, which is the other thing that makes it difficult to interpret, but compared [inaudible] vascular death, MI, stroke, CHF or TIA was 8.25% with naproxen and then about 5.5% with either celecoxib or placebo. So about a, you know, 1-1/2% difference.

Dan Lessler: And that would be different from…because the other data on celecoxib versus…or amongst data that's available there is…there are other randomized controlled trials with celecoxib versus Naprosyn and then…and in those RCTs the result is…

Roger Chou: Yeah, they were opposite. In the other studies celecoxib was associated with increased risk versus naproxen as well as versus placebo. And again the two main trials that that data comes from are these two long-term polyp prevention trials.

Dan Lessler: Okay.

Roger Chou: It's very…some of this…I mean every time something new gets published it confuses the picture even more, unfortunately.

Dan Lessler: Are there any other questions?

Alvin Goo: Hi, it's Alvin. In the study with the…in the patients with history of GI bleed do you know what was the timeframe of their last GI bleed before they were randomized?

Roger Chou: Yeah, I can tell you a little bit more about those studies. So both of those studies were conducted in Asia. I believe they were both from Hong Kong. I can pull…I think they were within several months, but I need to…I don't have the studies in front of me, but they were really pretty recent. These were patients who were considered to be, you know, very high risk.

Alvin Goo: Okay. Thanks.

Dan Lessler: I guess the other question I would have, Roger, is just also related to GI side effects. Looking at your slide 18 and the…I guess the second main bullet down about misoprostol, HS blockers and PPIs show a significant reduction in endoscopic gastric and duodenal ulcers with short-term use. You point out above that only misoprostol actually shows a decrease in serious events.

Roger Chou: Right.

Dan Lessler: I'm curious just…if the…that evidence is sort of similar to…I'm just trying to weigh that evidence, you know, think about it in terms of what's known about celecoxib and its reduction in…am I correct that only celecoxib has shown reduction in endoscopic ulceration? Not in definitive events?

Roger Chou: No. Well, the CLASS trial…so the CLASS trial is where we have most of our long-term data. And the CLASS trial actually looked at kind of clinical ulcers. So bleeding ulcers and complicated ulcers, so perfs and things like that. So there is actually data on, you know, what we consider clinical events, not just endoscopic events and then the meta-analyses actually looks at a clinical, you know, symptomatic ulcers. So it's not just looking at endoscopic stuff. So there is some evidence for celecoxib at least short-term for preventing…

Dan Lessler: Which is in the short, but not in the longer term?

Roger Chou: Yeah. I mean, you know, the problem…I think we've talked about CLASS for this committee before, but the CLASS trial was very problematic because they had a lot of dropout and the differences actually become non-significant after, you know, at 9 to 12 months partly because so many people dropped out. You kind of lose your power to detect differences anymore and no other trial really has been designed to look at long-term, you know, outcomes. The manufacturers of celecoxib, you know, basically say that there is no, you know, biologic reason why it would suddenly become ineffective after six months and, you know, our…kind of our response is that that may be true, but we just don't have the evidence that, you know, using the drug for longer than six months reduces clinical, you know, adverse events. So…and the observational studies, you know, that's where you hope the observational studies would help clarify things, but as I mentioned before it's…we actually get kind of mixed results from the observational studies with some showing, you know, GI protection and others kind of showing a neutral effect. So they don't really clarify the picture very much.

Dan Lessler: Thanks.

Vyn Reese: One other question. This is Dr. Reese. In the high-risk groups though it looks like celecoxib is really pretty much the same as a nonselective drug plus a PPI for those high-risk patients. So if you combine a PPI with a nonselective you end up getting the same risk. So they are high for both groups, right?

Roger Chou: Yes. You got about the same risk…there was about 5 to 6% in both groups and there was no significant difference. And those were rebleeds. So those were significant events.

Dan Lessler: Other questions for…? Roger, are you available to stay on line for just a couple more minutes? We just have a few stakeholders who are going to give comment and sometimes it's helpful to have you all around from OHSU to…

Roger Chou: Yes, I'm available.

Dan Lessler: That would be great. Okay. So we'll go ahead and do that. So again just to remind people I'd like to ask people to limit their comments to three minutes and please identify the organization you're with and whether or not you're sponsored. First is Dr. Effertz.

Bernie Effertz: Good morning. I was told that I would just have three minutes so I just prepared a one-page statement and it focuses mainly on cardiovascular risk. I think overall the message is that when you're looking at cardiovascular risk there is parity among the nonselective NSAIDs and COX-2 specific inhibitors and it's also important when you're looking at the data to make sure you're looking at which cardiovascular end point you're looking at.

Some of the data that the gentlemen showed was only focusing on MI, but if you look at a more broad definition of a composite CV risk the APTC, which stands for anti-platelets trial collaboration there they look at non-fatal MI, non-fatal stroke and death from cardiovascular causes and there we are seeing pretty much an odds ratio of 1.0 when comparing Celebrex to the others.

Also keep in mind that a lot of these trials aren't powered to look at CV risk. We're seeing end points in the neighborhood of 15 to 20 in these trials. If you ask a cardiologist who does these kind of studies I'll tell you, you really need about 500 end points to really be powered to make a statement on cardiovascular risk. Pfizer is going to conduct a trial that looks at that. It's called Precision trial. It started in September and it will be rolled out in 2010.

My goal in this statement is to differentiate the clinical reality from the media hype with respect to the CV safety and NSAIDs both nonselective and COX-2s. As background Vioxx was voluntarily withdrawn from the market in '04 because of increased incidents in CV risk versus placebo in an investigational trial called a proof for adenomatous polyps. Then in December the Disease Safety Monitoring Board for a trial that Pfizer was doing with the National Cancer Institute called ACP stopped that trial when they looked at the safety data and saw an increased cardiovascular risk. As a result of that they stopped two other trials that were going on at the same time. One was called PRESAP, also an investigational trial for colorectal polyps and ADAPT, which the gentlemen did mention. It wasn't in the earlier EPC report because it's very new, but that was also stopped and that was an investigational trial for primary prevention in Alzheimer's.

So in the EPC trial there was an increased signal looking at composite CV end points and that's the APTC end points. And it was elevated at 2.5% for Celebrex at 400 mg, 3% at 800 mg compared to 0.9% with placebo. In the other trial in PRESAP if you look at the APTC end points there was no statistical difference between Celebrex 400 mg a day and placebo. It was 2.3% versus 1.9%. Keep in mind with these polyp trials that there was no NSAID comparator. The comparator was placebo. However, in the ADAPT trial the comparator was Celebrex 400 mg and naproxen at an over-the-counter dose. It was naproxen 220 mg twice a day and placebo. And in that trial looking at a broader definition of cardiovascular end points it was like the gentlemen said 5-1/2% with Celebrex, 5.7% with placebo and 8.2% with naproxen.

Then there were also several case control studies. These are observational retrospective data mind and one published by David Graham who was the whistle blower in the Vioxx case, another by [inaudible] Cox and in those studies they showed that there was no significant difference in a composite CV end points or odds ratio between Celebrex and nonselective NSAIDs. The odds ratios were 0.84 and 1.21 respectively.

I guess I'd just like to summarize by saying that since this happened with the Vioxx withdrawal and the stoppage of the Celebrex polyp trial the FDA conveyed a joint committee of the Arthritis Advisory Committee and went through the data and their charge was to look at the risk benefit of COX-2s and nonselective NSAIDs and they voted 31 to 1 that the overall safety risk benefit of Celebrex warranted continued marketing in the U.S. Since that time Celebrex has received two more indications. It received an indication for ankylosing spondylitis and then just last Friday it's been FDA approved for the treatment of juvenile rheumatoid arthritis in patients two years and up.

Dan Lessler: Thank you. Are there any questions? No? Okay. Thank you. Next is Dr. Kinahan.

Peter Kinahan: Thank you chairman and committee. First of all I'm an orthopedic surgeon. I'm a general orthopedic surgeon from Everett, Washington and I'm not being sponsored to be here. Forty percent of my patients are Labor and Industry patients and I'm really here because I want to ensure that my patients can continue to get access to the medications that I feel they need.

There are three major patient groups I'm concerned with. One is the patient's who are coming up to the time of surgery. I think that celecoxib offers them a great opportunity to continue on their medicine right up to the time of surgery because it does not have any antiplatelets activities. So sometimes if people are on a regular anti-inflammatory you're operating on them doing a hip or a knee replacement and even an hour after the surgery their skin edges are still bleeding because their platelets just don't work and with Celebrex that just does not happen. It's a really good medicine for that. The other thing is that if the patient's go into surgery off of their anti-inflammatories they have a lot more pain before surgery, they have more pain afterwards and they use a lot more narcotic painkillers. There are good studies that show using fairly high doses of Celebrex perioperatively, decrease the narcotics that the patients need afterwards and decrease the narcotic side effects. The long-term patients there's some talk about whether or not these effects of the Celebrex or the risk…the decreased risk of GI side effects continue on after six months. I've had many patients on Celebrex for five years or more and I never, ever have to have them stop the medicine because of GI problems. The number of patients who told me, "You know this is a miracle drug because I can continue to take it." When they give them a prescription for Naprosyn or ibuprofen they might take it…a lot of people take it for a week and then they stop taking it for a week or two to let their stomach settle down and that yo-yoing just does not happen with this medicine. The other issue is a gain with cardiac patients of low-dose aspirin whether or not the other anti-inflammatories interfere with the aspirin and do not help with the cardio protection. Anyhow, I'm going to keep it short. I'd like to thank you for taking the opportunity to give my speech. Thanks.

Dan Lessler: Any other questions from committee members for Roger? No? Okay, Roger, thank you very much. We appreciate your time.

Roger Chou: Thank you.

Dan Lessler: Take care.

Roger Chou: Bye, bye.

Dan Lessler: So maybe once again we can look…just begin with our previous motion. You people can…right, which we voted on and then we rescinded them. I guess we left it moot. So maybe we could just open it up to comments and discussion here. Observations?

Vyn Reese: This is Dr. Reese. It's a very complicated area and the more data we get the more confusing it becomes. It looks like perhaps celecoxib might be less GI toxic, but in the long term the data's really not in. You can't be sure. In high-risk patients it's about as toxic as a regular NSAID…as a nonselective NSAID and a PPI. So in patients who can't tolerate regular NSAIDs a lot of times adding a PPI will make them be able to tolerate those drugs. So the question is is it different from that combination? Cardiac risk is up in the air, too between the two groups. Naprosyn was looking like the safest drug in this entire group and then the latest study made…there is some question about its safety as well. It's a tough area to look at and to really…we don't have enough evidence to know which of these drugs is the safest. It's a complex area. Whether we should have celecoxib on the formulary…is it enough safer than the other drugs to include it…not placed on the formulary that to me is unclear. The data is not there. In the elderly I'm afraid of every NSAID to be honest. I don't use them. I'd rather have them use a low dose narcotic to be honest, they are safer. And so if it's a chronic pain problem the NSAIDs can be very dangerous in high-risk groups. With congestive heart failure and patients like that NSAIDs have caused lots of hospital admissions, all of them. So it's a very difficult area to look at and I'm still perplexed by it as we were when we tried to get a motion a couple of years ago.

Dan Lessler: Siri, how are these drugs currently handled by Medicaid?

Siri: All of the nonselective NSAIDs require expedited prior authorization and we require that there's not a history of a GI bleed before we will pay for these drugs. The COX-2 inhibitors are also on expedited prior authorization for history of GI bleed and cardiovascular events or history of a cardiovascular problem. And then it's really specific to their FDA labeling as far as dose and indication and duration of therapy. So the COX-2 inhibitors are covered, they're all covered, but they do have expedited prior authorization that's required.

Dan Lessler: Thanks. Wondering if there are other observations or comments about this class? Bob?

Bob Bray: This is Bob Bray. It just seems to me that even though there are a lot of questions that are still out there we have COX-2 inhibitors and everything else as being able to differentiate between the two of them. And so I would suggest that we craft a motion that basically takes the partially selective and nonselective events and put them together because I don't think the evidence is clear that there is any one that is less safe than another and I think that COX-2 inhibitors with the information we have with them do put them in a different situation and I would propose that we leave that the same and have them be available on expedited prior authorization.

Man: Do you want to make a motion?

Dan Lessler: So we will deal first with the nonselective and selective separately. I think that's a good idea. Are there any other comments or responses to Bob's thought here? So do you want to…so we can first do the nonselective. Do you want to try to craft a motion?

Bob Bray: So after considering the evidence of safety, efficacy and special populations…and here I would just take out the specific treatment indications. I don't think we need to mention those. I move that…and here I would insert everything except celecoxib, tiaprofenic acid and tenoxicam. So basically stick them all in there and then take those three out. Okay? Are safe and efficacious. No single non-steroidal anti-inflammatory drug is associated with fewer adverse events in special populations. The NSAIDs can be subject to therapeutic interchange in the Washington PDL. Eliminate the very end for the treatment of.

Patti Varley: This is Patti Varley. Am I allowed to ask a clarification point?

Dan Lessler: Yeah.

Patti Varley: And maybe it's just how I'm hearing or reading it this time, but when Siri was saying how right now it's an expedited prior authorization with clarification of no history of a GI bleed. When I see this written like this and it says, "Is associated with fewer adverse effects in special populations." Isn't people with GE bleeds a special population or am I semantically interpreting that differently?

Bob Bray: In my mind you can make them a special population, but I think what's being said is that it's probably not an appropriate drug to use in that population whether they are selective or nonselective.

Dan Lessler: Right.

Vyn Reese: Those were high-risk patients. It's not…I mean I don't know if it's a special population. It's a patient with another illness. It's…I mean usually select populations often are different ethnic groups. I mean that's what we've usually been using that phrase for. So I'm not sure…

Patti Varley: Yeah. That's why I was asking sort of semantically what we mean, but I haven't had…we haven't had very many other drug classes where we have had a criteria that specific before approving a drug that I can recall. Where that is a specific criteria and I don't know if we need to address it in this motion or not.

Jeff Graham: This is Jeff Graham. In the meta blockers we do have that. Carvedilol is specifically for…what was it for? Some level of congestive heart failure. Stage 3 to 4…so we were explicit in that.

Carol Cordy: Carol Cordy. I…are there studies that show that there is an increased risk of GI bleeds with people who have had that history? Because it's increased for everybody, but it is…have there been studies?

Dan Lessler: That people who have a history of GI bleeding are at higher risk then…? Yes. I think that's pretty well documented.

Patti Varley: Isn't it a contraindication for people who have histories of GI bleeds?

Dan Lessler: I would say, yes. I mean in some sense there can be a relative contraindication, I suppose. At some point you're weighing the risks and benefits, but I think it's well known that in somebody with a prior history of GI bleed I think there's…and even the evidence that was presented here, I think, confirms that. As to whether or not that's a special population I guess…I mean I don't know whether…I think maybe, Bob, I would tend to agree that I don't really see it as a special population. I mean we…there are other medicines, you know, for example that are contraindicated in renal failure or something. At some point you're dependent on the prescribing clinician to know what the appropriate use of the medication is and when is it contraindicated? I don't know that there's…and there are other times, you know, again particularly when somebody has some degree of renal insufficiency that, you know, one or another drug that you would use…normally use in somebody who had normal renal function you should not use. So, you know, it's not…

Siri Childs: This is Siri Childs. Last time we brought this up we actually had a discussion in the minutes and so we had clear direction and occasionally we have to go back to your minutes to show that our…the recommendation is that it not be given to someone with a history or someone, you know, with a GI bleed. If you would like to add that to the motion it would probably help us in making sure that that doesn't happen.

Dan Lessler: Actually, then there's something I would bring up here having spoken with my colleagues at Harborview, which is while I fully agree that these medicines are contraindicated and patients with a history of GI bleed I think operationalizing that currently for Medicaid is problematic because at least what happens in our facility is that the patient is asked by the pharmacist, "Have you ever had a…?" And if the patient…if the patient answers yes in any way, shape or form then, you know, the medicine is not prescribed and quite often, you know, it's a history when you go back and take a look. It's a history of reflux disease or something like this. So there's…so I agree in principle, I just…I have a lot of concern and this will come up actually when we reconvene as the DUEC in terms of the problems that I think we all face in terms of management of pain because we're, you

know, we're increasingly being held accountable, appropriately, for managing pain on the one hand, but we're…our options are being increasingly constricted on the other.

Siri Childs: It requires prior authorization and the pharmacists are required to ask that question, but then it will come to…if the answer is yes they have had a GI bleed then it comes to our prior authorization program and we panned to the doctor for additional information. And if the doctor verifies that there has been a GI bleed then we do deny it, but the doctor has the opportunity to clarify it at that time.

Alvin Goo: Yes, but sometimes that can take quite a while. There's a delay of at least a week.

Dan Lessler: I don't know whether for other people who prescribe these and Carol or Bob or Vyn whether this has been an issue for you guys?

Vyn Reese: I haven't asked about GI bleeds that I'm aware of before. It should be a contraindication. I agree that it should definitely be a contraindication. If the patient really has a history of a GI bleed and the doc missed it…and I had this happen in my clinic when a rheumatologist gave a prescription, missed it, the GI bleed and the patient bled again. So it's like it's…it does happen and the doctor misses it. So there are both sides of the coin there and it's not a good situation to give one of these drugs to a patient who has had a major GI bleed before. If they had bleeding hemorrhoids that's another issue and that's what some patients will tell you. So it's, you know, it's complex. I would sort of error on the side of safety. If somebody told me that they had a GI bleed before I would probably not prescribe these drugs.

Patti Varley: This is Patti Varley again and as I was listening to Alvin and your comment that came down to my question is that is it more inconvenient for the patient to wait a week to get clarification about whether this is safe or not or less safe for them to actually have another GI bleed? So to me that was my bottom line too is it came down to a safety issue.

Siri Childs: Dr. Lessler?

Dan Lessler: Yes.

Siri Childs: If Dr. Jeff Thompson were here he would probably remind the DUEC, the old DUEC members that in 1999 and 2000 we contracted with Washington State University to do a Pharmaco economic study on the GI bleeds associated with NSAIDs and what we learned in that study when we compared the use in 1998 compared to the use in 1999/2000 is that after we implemented this EPA criteria for the pharmacist to ask, you know, and screen for a GI bleed we dropped the number of hospitalizations for a GI bleed in Washington State in our Medicaid clients by at least 22 patients and it saved our state $2.5 million. So we felt that it was pretty justifiable that it was really more wide spread than what we had thought and just coincidentally there was a little cohort to that study because the COX-2 inhibitors were introduced right about that same time and so we followed our COX-2 inhibitor patients and we found an equal number of hospitalizations for serious GI bleeds as well.

Vyn Reese: I agree with Siri. This is Dr. Reese. You should have…these drugs are contraindicated enough for gastrointestinal bleeding. I think that needs to be part of it and so I would want to modify it to say that. And I think waiting for a week for an NSAID prescription in somebody who has had a previous bleeding ulcer it's worth the wait. I mean they could take something else for that week. NSAIDs aren't an emergency. I mean nobody has ever died before they didn't have an NSAID for a week. It's not like an antibiotic or something that's for an illness that has to be stopped immediately. I think a week…if that's what it takes…in my experience it's been less time than that, but if you have to wait a week that's worth it to prevent GI bleeds and these drugs are dangerous. They are definitely dangerous.

Siri Childs: Dr. Lessler?

Dan Lessler: Yes.

Siri Childs: May I say to everyone in this room if anyone is waiting a week for a prior authorization approval I want you to call me. Let me give you my number right now (360) 725-1564. You should never have to wait that long and I will help you if something has gone awry.

Patti Varley: And she really does.

Dan Lessler: Okay. So thank you, Siri for the information. So it sounds like we would maintain the motion as is plus modify it to include that these medicines are contraindicated in people with a prior history of GI bleed, which would then maintain the current system of prior authorization.

Carol Cordy: Carol Cordy. On one of the previous motions we left out safe and I'm just wondering if we should, or could leave out safe and then put the…whatever additional. They are efficacious, but they are clearly not safe. Or are we just saying they are equally safe?

Bob Bray: This is Bob Bray. I think we problem we have is we really don't know the information that says they are equally safe. I mean some of the information we're being given is that they are, you know, some say there may be a differentiation of safety with one versus another. So equally safe I don't think would be truly accurate. I would not object to a consensus that says that we take the safety part of it out since that is a question.

Dan Lessler: Any other?

Carol Cordy: Then you can't say that none of the associates with fewer adverse events because we don't know that either.

Man: Delete?

Dan Lessler: Delete. Right.

Bob Bray: I don't think the evidence is clear.

Dan Lessler: Okay. Any other comment or modification? So maybe we can just…review it from the…without reading all the individual…

Bob Bray: So after considering the…this is Bob Bray, again. After considering the evidence of safety, efficacy and special populations, I move that the partially selective non-steroidal anti-inflammatory drugs, those three listed, and the nonselective non-steroidal anti-inflammatory drugs, those listed, are efficacious. The NSAIDs are contraindicated in patients with a history of GI bleed…do we want to say upper GI bleed?

Vyn Reese: Upper gastrointestinal bleed and spell it out.

Bob Bray: Upper gastrointestinal bleed. The partially selective and nonselective NSAIDs can be subject to therapeutic interchange in the Washington Preferred Drug List.

Dan Lessler: Okay. Is there a second?

Man: Second.

Dan Lessler: Okay. Any other further discussion? Okay. All those in favor say, I.

Group: I.

Dan Lessler: Opposed, same sign. Okay. So now we're…did you have a comment, Jeff? No? Okay. We're on to the…well, just celecoxib really in terms of the discussion at this point.

Vyn Reese: I had a question for Siri . Now how is it set up now with celecoxib? Do they have to have…just give me what the prior auth, you know, sort of the little verbatim thing that they have to go through.

Siri Childs: Okay. For celecoxib the EPA criteria is first no history of a GI bleed, and then we added the cardiovascular history as well to that one. And then each…for each indication for Celebrex we have the dose range and the indication and the duration because what we know about these drugs is that if you increase the dose they become nonselective. So we want to, you know, deal with the known and keep them at their FDA label doses.

Vyn Reese: Do we have to put a separate motion for celecoxib or I mean how does it…do we have to have another motion or do we just leave it the way it is and we don't make a motion?

Siri Childs: Well, what I usually say to folks when I'm describing it is I say that celecoxib is on EPA for a specific…well, for the history of GI bleeds and cardiovascular events and for specific FDA labeling for dose indication and duration. I don't know if you want to say all of that or not.

Dan Lessler: So when you say on EPA for…

Siri Childs: Dose.

Dan Lessler: For cardiovascular events…can you clarify what…so if somebody has a history of…would not…

Siri Childs: Uh huh.

Dan Lessler: Okay. Same with somebody with a history of GI bleed then?

Siri Childs: Uh huh.

Dan Lessler: Okay.

Siri Childs: But again for all of the COX-2s when they were all there we were very careful…I mean we saw some of those warning signs really early on and we were very careful to hold the dose at the FDA dose so that we wouldn't see it creep up and we had all sorts of requests for dosing outside of that dosage range, but for our Medicaid clients they never got anything above that. So…

Bob Bray: This is Bob Bray, again. So Siri if we just stop here and don't say anymore then celecoxib would continue as an EPA at those criteria?

Siri Childs: I'd like you to say that so that we would have that continued authorization.

Bob Bray: Okay. Motion number two.

Siri Childs: Continue with your present criteria for safety.

Bob Bray: I would move that celecoxib continue its current EPA criteria…or current availability on expedited, prior authorization. Let's say that.

Alvin Goo: Hi, this is Alvin. Just for clarification on the cardiovascular disease. Is that high risk of or history of?

Siri Childs: History.

Jason Iltz: This is Jason. And that's why I think, you know, today is probably not the place, but at some point that EPA criteria needs to be revisited and say, "Is this still appropriate or should we add something? Should we take something away?" Because I think what I heard today I'm not sure that that really is a good reason to prescribe maybe that medication over something else. So I just think we should look at that. I do think we need to…in my mind when we're going through this I was sort of thinking that we were going to make a second motion that would include what Bob just said, but then also says what we said above with the difference being that it's not subject to therapeutic interchange. Is that…I mean I'm thinking we need to at least state that it's efficacious because we left it out of that statement for the selective…

Donna Sullivan: This is Donna Sullivan. I need to know for Uniform Medical Plan and I would imagine Jamie might need to know for Labor and Industries, are you saying it's non-preferred except for it should be available to people with these indications? Or this special population? Or is it preferred and restricted to these people with these populations? Because currently it is a non-preferred drug.

Vyn Reese: This is Dr. Reese. I think it's non-preferred. It should remain a non-preferred drug and that prescribers can prescribe it if they have prescribing authority. So I don't see…I'm still not sure if it's safer in patients who had prior bleeding ulcers. I'm still not sure if it's safer in patients with cardiovascular disease. I'm still in the dark as to all those indications. I'm not sure if it's safer or more dangerous than the other NSAIDs at this point. I mean the more I know about it the less I know.

Duane Thurman: You know, this is Duane Thurman, I don't want to make things more complicated but I think that there are two issues here. I think that the one thing you need to do in your role as the P&T Committee is make a determination of whether these drugs are included in the review and you've said specifically they should not be preferred and that brings in the question of whether the dispense as written override will apply to endorsing practitioners, and then I think to the extent you want to tell HRSA to keep doing what HRSA is doing that's something I think you would do in your role as the DUR committee, but I think the basis of your decision is are the drugs on or off the preferred drug list? Or are they non-preferred on the preferred drug list? Because it will have an impact on how you'll treat a dispense as written script from an endorsing provider. I mean, Siri , is that…

Siri Childs: I think you're right. If they would designate it as a non-preferred we would have prior authorization criteria that would identify all these things, too. So, you know, and we expect that they will tell us, you know, what category to put this in so if they would just say non-preferred for this criteria we would handle it that way, too. As far as this EPA criteria is for safety and DAW does not override it, you know, they have to meet this criteria.

Duane Thurman: Any comments from Don or Jamie on what you need for direction?

Dan Lessler: So if we just…if we just said celecoxib should remain non-preferred would that…and just stop there.

Siri Childs: We would definitely develop criteria for its use and it would just exactly what we have now.

Dan Lessler: I don't know how others feels, but I would propose at this point just saying that it should be non-preferred. I think that's the cleanest way. Are there any thoughts about that?

Donna Sullivan: This is Donna Sullivan. Just for simplicity sake do we want to just add it to the list saying it's efficacious and then as a caveat say it should be non-preferred?

Dan Lessler: Sure. We could say it…

Donna Sullivan: You don't say it…you took out the safety…and then revote on the previous motion.

Vyn Reese: That's what it says right there.

Donna Sullivan: This is actually a separate motion. We're developing a new one. Can we add it to the previous motion and then just re-vote on it?

Dan Lessler: So add that on to the tail end of the first motion.

Janet Kelly: Donna, this is Janet Kelly. Up in the top we specified…top of the motion that it was the partially and nonselective. So if we just remove that and say non-steroidals then we will be fine, but right now we have…

Donna Sullivan: Okay.

Alvin Goo: Then we get into an issue with the…

Donna Sullivan: Well, we don't want them substituting.

Dan Lessler: Yeah, I would just…right.

Donna Sullivan: This is what I was talking up here…is where…I can put that Celebrex should not be interchanged. Is that what you want?

Vyn Reese: Right.

Donna Sullivan: If it's a non-preferred drug we would…what would happen is one of the other anti-inflammatories would be dispensed instead. Is that what you intend? Or you don't want Celebrex to be used?

Bob Bray: This is Bob Bray, again. What I was thinking you're suggesting is that we leave the prior motion as is and at the very bottom of it state that celecoxib is efficacious and should remain non preferred. Because then we don't have to change the rest of the stuff above. I think it makes it a little cleaner.

Vyn Reese: I would agree with that.

Duane Thurman: And I guess…this is Duane. The final issue though is whether you want to add something limiting the therapeutic interchange of that drug? Non-preferred and not subject to therapeutic interchange? Or…

Bob Bray: Correct.

Dan Lessler: Right. Celecoxib is efficacious and…

Carol Cordy: Carol Cordy here. I think you need to put back in the partially selective and nonselective that you took out.

Alvin Goo: So just for a point of clarification then if you…if a provider does prescribe celecoxib it's going to have to be denied and nothing will be substituted and then it will have to get reviewed if it fits the criteria.

Dan Lessler: That's correct.

Siri Childs: Can I comment on that?

Dan Lessler: Sure.

Siri Childs: Right now ACS is handling celecoxib with all of their criteria, you know, and the way it is all set up is all of them have to clear the EPA criteria first and then celecoxib requires that specific criteria, but ASC handles it.

Alvin Goo: Okay. Will that be okay with L&I and Uniform?

Donna Sullivan: For us it will just be covered as not preferred and beginning in 2007 we are implementing anyway a step therapy for non-endorsing providers that they have to have tried and failed two of the other 16 generic NSAIDs.

Woman: For L&I we don't we don't have EPA so it would be a straight PA. So there is no opportunity for a pharmacist to interchange that prescription for another non-steroidal. It will be straight PA and then it will require a call to us and then we'll go through the criteria.

Jason Iltz: This is Jason. So that's the question I have. Can we as a committee help facilitate that, but not open up any unintended consequences going the other way? So for example when you have the patient hand the pharmacist the script for celecoxib if the pharmacist says, "Have you had a bleed? Do you have cardiovascular problems?" And they say, "No." Doesn't it make more sense right then to have them interchange it to an NSAID that is on formulary as opposed to having ACS or somebody

else having to handle it administratively? Is there a way to facilitate that, but not have the other thing come in where a patient comes in and says, "Oh, I want that because I saw it on TV"?

Woman: The way to do the interchange is through the therapeutic interchange program. So I just heard you folks restricted the celecoxib prescriptions to not having that ability. So that's how it's going to be resolved.

Siri Childs: And Jason it would go to ACS because it's part of that drug class and that's our contracted vendor. So we wouldn't handle it in-house anyway.

Jeff Graham: Duane, this is Jeff Graham. Couldn't we ask…since this is not going to be implemented…the earliest would be July 1, 2007, we have said that it is non-preferred. Couldn't we ask the agencies to come back at our next DUR meeting and give specific recommendations of what they think? And you may have some at that time that would work. Rather than trying to figure it out right now with three agencies talking how it might or might not work.

Duane Thurman: I think you're right. I think the main thing we need to do is we need to have guidance to the three agencies from the P&T Committee in terms of how this works and when you talk about therapeutic interchange we're talking about it within the context of our unique preferred drug list dynamics with the endorsing and non-endorsing practitioners and so I think that at this point you've given the agencies enough information as to how to implement the drug classes and I think to the extent they are non-preferred and therapeutic interchange does not apply that at this point it's up to the agencies then to formulate their internal normal procedures as to how those stops will work and to the extent that HRSA believes it needs to come back to the DUR board for more information or if you want more information then we can facilitate that. Does that sound reasonable?

Siri Childs: Was there just the one word change from history to risk of? There's more?

Alvin Goo: It had to do with the denial of therapeutic interchange for L&I.

Siri Childs: Oh, okay.

Dan Lessler: Okay. So maybe we could just review this one more time and…one last time, Bob, since we…make sure we're all on the same page.

Bob Bray: After considering the evidence of safety, efficacy and special populations I move that the partially selective non-steroidal anti-inflammatory drugs, those three listed, and the nonselective non-steroidal anti-inflammatory drugs, that group listed, are efficacious. The NSAIDs are contraindicated in patients with a history of upper gastrointestinal bleed. The partially selective and nonselective NSAIDs can be subject to therapeutic interchange in the Washington Preferred Drug List. Celecoxib is efficacious and should remain non-preferred and not subject to therapeutic interchange.

Dan Lessler: Okay. Is there a second?

Vyn Reese: Second.

Dan Lessler: All right. All those in favor say, I.

Group: I.

Dan Lessler: Opposed, same sign. All right. Very good. It passes. So can we adjourn until about 2:30? Would that be okay Siri ?

Siri Childs: Yeah, that's great.

Dan Lessler: Okay. And then we'll reconvene as the DUR. [end of Side A]

[Side B]

Dan Lessler: We have those in our binder under tab "DUR Minutes". If people could just maybe take a minute and peruse those. And is there a motion to approve the minutes? It's probably best if it was somebody who was here. Right, so that's one correction to the minutes.

Jason Iltz: This is Jason. I'll move to approve the Washington State Pharmacy and Therapeutics DUR Board Meeting Minutes dated October 18, 2006.

Dan Lessler: Is there a second?

Man: Second.

Dan Lessler: All those in favor, please say, I.

Group: I.

Dan Lessler: Okay. Minutes are approved and we can move into our afternoon agenda here. So…actually, I know Dr. Gary Franklin who…Gary's been here before presenting to us. The Medical Director for L&I is here and I think the main purpose of the agenda this afternoon is to talk about a guideline for prescribing of opiates in non-malignant pain and maybe before you get going, Gary; Siri , I didn't know whether there was any other comment from…in terms of setting up this discussion that you wanted to make?

Siri Childs: Well, I would like to introduce Mr. Scott Best. He is going to present some data regarding Medicaid patients who have been on high doses of the long-acting opioids or the opioids in conjunction with Dr. Franklin's presentation.

Dan Lessler: Great. And I think…Gary, I believe you were going to present first and then I know you've got another meeting that you've got to…just in terms of…because I think we want to know just for gauging discussion, what time do you need to leave?

Gary Franklin: I probably need to leave by about 3:15. I'll try to sort of semi hustle through these slides and then we can maybe have a little discussion and then there would be time for Scott. I guess we could have done it the other way around, but I have a 4:00 at the U. So I…

Dan Lessler: Okay. Take it away.

Gary Franklin: Okay. So I was here probably now about maybe a year and a half ago. The Agency Medical Director's Group…we're probably the only state in the country where the agency medical directors of all the agencies, health care agencies, actually meet on a regular basis. I chair or co-chair that meeting and have for some years now. So in 2003 House Bill 1299 passed and asked the agencies to collaborate on formal assessments. The P&T Committee, I think, was established the same year in 6088. And then in 2004 there was a budget proviso. Is that right, Jamie? Was that 2004? Budget proviso that said that the agencies could actually work together on treatment guidelines. And so we took the opportunity of the next summer to work on a…and you might remember this, an off label neurontin guideline that we presented here for discussion and so this is the second inner-agency guideline that we are presenting. I'll talk about the whys.

We started meeting with a group of…large group of pain clinicians early in the spring and we've now had five or six meetings all together with this…I'd say 12 to 20 pain experts from around the state—opiate experts, people that treat a lot of patients with chronic pain, you know, lots of people from the university including Dr. Lozure and a number of others who are experts in this area. The reason was is that we became concerned several years ago because of a disturbing pattern of increasing deaths from opiates. We started noticing in L&I probably in 2001 or so deaths from accidental overdose of opiates that we had never seen before. These seemed to be associated both in the individual cases, as well as when we started looking at it more systematically with rather dramatic increases in doses of particularly schedule II opiates. So a couple of years ago we at L&I took a formal look at…we got all the death certificates we could on all the known deaths that we could identify at L&I among injured workers that had died and identified 32 definite or probably

deaths among injured workers primarily between ’97 and 2002 and then I’ll show you another graph in a minute, which is statewide data that reflects the fact that this is not only happening in L&I, but statewide big time since 1998. You might remember that in about ’98 almost all the states, including our state, went from a policy of you can’t use opiates for chronic non-cancer pain. Literally you could not and probably dramatically under treating people to passing laws and regulations that dramatically turned things around to, you know, the door swung 180 degrees to you may treat chronic, non-cancer pain. And you might remember the regulations that came out and then L&I published some guidelines, but when that happens most of the principles in all of those guidelines and principles were principles that the whole world agrees on and are reflected in the WHO document for using opiates for chronic, non-cancer pain such as, you know, use a single…a prescribing physician uses a single pharmacist, sign a, you know, some kind of a contract that you’re going to behave in a certain way. Everybody agreed on all of that stuff, but one thing that did not happen at that time was any guidance whatsoever on dosing. I think (a) no agreement on anything like that, and (b) there were probably some quarters in the country that didn’t want to see anything like that. So that never happened and the other thing when that policy changed back in the mid to late ‘90s it was based on very flimsy data as to what taking chronic opiates…opiates chronically for chronic non-cancer pain what that would do. There’s no evidence for example that pain and function improve as you are taking these things for months and months on end or years on end. That pain and function improves as you are increasing the dose. There’s no solid data on that. In fact, there’s some data that while pain improves tolerance develops dramatically in some people and then the dose goes up, but function does not improve. There’s not a lot of evidence that function improves as that is all going on. On the other hand there’s not a lot of data either on, you know, who can take chronic opioids and keep a dose at a reasonable level and function. There’s not a lot on data on that.

When L&I discovered these deaths a couple of years ago we actually sent a letter out…a warning letter to all the doctors that L&I providers…it was like a red warning letter saying, “Please be care. Please pay attention to these guidelines as to how you’re using the opiates.” And actually didn’t get too much feedback on that letter, but it was…we were very concerned about it because as far as I’m concerned, you know, as the Medical Director at L&I I haven’t seen too many worse things than somebody coming into L&I with a back sprain and dying from an accidental overdose of opiates five years later. I don’t see too many things worse than that. I mean failed back surgery syndrome is terrible, but there aren’t too many things worse than somebody coming in with a relatively, you know, non-catastrophic minor injury and dying from an accidental overdose of opioids.

Next slide. So this is data from the Health Department. They took the same criteria that we used in the paper that was referenced in the last…so we published our worker’s comp deaths as you can see on the previous slide. Just in 2005 in the American Journal of Industrial Medicine and then since then the Department of Health has also been looking at statewide patterns of death from unintentional prescription…or actually unintentional poisoning deaths and then within the unintentional poisoning deaths the prescription drug associated deaths. What you see here is a subset of the deaths gotten from the Department of Health death records and you can see that the deaths have just risen dramatically since the late ‘90s. The same patterns have been seen now across the country and in the reference on the previous slide by Paulozzi from the CDC had some things just like this from around the country. So this is a pattern that has been occurring in worker’s comp, it’s been occurring statewide and it’s been occurring across the country.

You can see that the…if you use some criteria like we used in our paper to identify from a death certificate, you know, is the death related to opiates? Is it sort of probable or definite? Or is it just sort of possible? Or is it questionable? And we tried to use some conservative criteria to identify the definite and probably deaths and what we did was if…even if the death certificate said that it was, you know, that it was accidental overdose and that it was opiates that if there was any mention of an illicit drug or if there was any mention of alcohol we did not include it as a definite or probably death. So we used very conservative criteria. I didn’t want to be criticized for, you know, sort of overdoing it on who we called an accidental opiate death, but you can see here that using even the definite criteria because the Department of Health used the same criteria that we used, that the only…that the two groups that are increasing dramatically are the definite and possible prescription drugs, that’s not the illicit drug deaths—they’ve been pretty stable. Also if you look at countrywide suicide deaths have not dramatically increased. So you could argue about how the

medical examiners are labeling these cases, etc., etc. and I can tell you, you know, unless there's a suicide note they're not going to call it a suicide basically. So there might be a little crossover here between these accidental overdose deaths and some suicides, but I don't think that that is a highly expected pattern here because of what we know about the suicide rates around the country.

So given this background we called together the pain experts that I mentioned to you earlier in the spring and we got them to agree to work with us over probably about four meetings, but it actually took five or six meetings to develop a guideline on opioid dosing. At the beginning of that conversation, the first two meetings, the main idea was to do…the main part of the guideline was the opioid dosing part, but then everybody agreed that we really needed sort of a part two of the guideline that would also provide a little bit of guidance for patients that were already on high doses. So the main goal was to provide some best practices for management of patients in part one that were just transitioning from acute to sub acute to chronic pain. That's the main goal here was to prevent these terrible things from happening in patients by educating doctors as to better ways to think about escalating doses as, you know, as you're transitioning someone from acute to sub acute to chronic pain. The goal here was, you know, how can you figure out a way as Jeff Johnson wants to say, take a deep breath. If you've gotten up to a certain dose and pain and function have not continuously improved that's the whole goal of pulling these people together and of course the main issue here was, you know, what's the dose gonna be? We'll get to that in a minute.

So one thing that the guideline was not going to be and this again was all agreed up front. This is only a guideline for dosing in chronic, non-cancer pain. It is not a guideline for the treatment of cancer pain or end of life care or hospital care or anything like that. It's only for chronic non-cancer pain, that it is not an attempt to set a standard of care related to board actions and it is not a dosing limit in terms of a firm dosing limit that the agencies are going to slap, you know, someone's hand on or just stop paying for opiates. The intention and this sort of evolved over several meetings that this will be an educational pilot. So the rollout of this guideline will be for educational purposes and all of the agencies will develop…we are right now developing a work plan for the educational pilot, which will last a year from the time that it's rolled out, hopefully in January and that we will also build into this a formal evaluation plan for how we're going to evaluate the impact of the educational pilot or rolling this thing out. But of course the main goal is to prevent these rapidly escalating doses and the development of severe tolerance that might put people at risk from dying from opiates.

So the main purposes are to improve care and the safety with opioid treatment for chronic, non-cancer pain and to assist the provider when starting a transitioning to patients to assist in assessing and monitoring and part two really talks about the…the main part of it talks about how to wean opioids if that's indicated. It's also to assist the provider in optimizing opioid treatment for patient's who are above the opioid dosing threshold by primarily obtaining a second opinion or an additional…to get some expert input to the primary care doctor if a threshold has been reached and…

Next slide. Is the actual dose on one of these slides, Jaymie?

Jaymie Mai: I don't think so, but you should all have the actual guidelines in your packet.

Gary Franklin: You should the [inaudible] in your packet and you can see in the guideline on like, I guess, bottom of page one, top of page two, that the agreed upon…actually the whole discussion started out with, well what does…once you start getting concerned at if the dose is going up and pain and function is not improving? And actually the initial range that the group came up with was 60 to 90 mg, you know, that was an okay upper limit of a range, but they started getting concerns about…that it wasn't high enough, that there's so many people out there on so many higher doses than that that, you know, you need to have a little more [inaudible] room in here even with new patients, you know, opioid naïve patients. So they ended up with, you know, complete agreement on this that it would be 120 mg…that the threshold dose for obtaining a pain management consultation for assistance at to what, you know, better ways that they might be able to do this or paying attention to comorbidities that they didn't recognize or other things that are going on here if pain and function have not continuously improved. If they are documenting that pain and function is improving even at 120 mg it doesn't matter. They can keep going, they don't have to get a pain management

consultation. And then in the guideline also are references and resources for various kinds of instruments that can and should be used to track pain and function in these patients.

Vyn Reese: Can I ask a question at this point?

Gary Franklin: Yeah.

Vyn Reese: Why would it be pain management consultation? Why not…there are other consultants that this be a neurology problem, it may be an orthopedic problem, it may be a psychiatric problem and I've been uniformly unimpressed with my pain management consultations that I've seen to the University and other pain clinics as to how useful they are. Usually they come back and say, "Increase the opiates," and so I think that other consultants…you may have made this guideline with those groups involved, but I'd say other consultants are often much more helpful than the pain management consultant if it's an undiagnosed condition. So I think that you should include, which is on page 4, consultation may be with but not limited to a physician specializing in psychiatry, neurology, anesthesiology, pain, physical medicine, rehabilitation, orthopedic addiction medicine, rheumatology or oncology. I think a larger list of consultants at that point is advisable. I think certainly if you're escalating the opioid dose and you're not sure what's causing it and it could be something else you may need a consultant, but to limit it to pain management consultants, I think, is too limited. I would broaden that…I would bring that consultation requirement up to a broader level of consultants.

Gary Franklin: Thank you. It was brought up to a broader list. We started out with a very limited list of kinds of specialty that have certain certifications and that is the main starting point, but that is brought up and that list you see there is a much broader list than we started out at. And, you know, I think that you can't have everyone on this list and actually we hope to publish a list of people that are willing and able to do this kind of thing at the beginning of this. We had a public hearing on this and one of the main feedback things from the public was they wanted to see, you know, who might be available and willing to do this kind of thing. But I would say that not everyone really has the expertise to look at the opioid issue. You might have the expertise to look at a comorbidity, but you might not have the expertise to, you know, understand opioid pharmacology, etc., etc. It's a point well taken.

We did expand the list, the list is dramatically expanded from what it was originally. The group was basically not to go so far as to say, you know, if someone self-identifies themselves as a pain management expert and they don't have any extra training or any specialty related to that or anything else then how do you know they are a pain management expert? You gotta have some kind of guidance here and so remember that this is an educational pilot and we're going to be looking at things such as is the availability and the appropriateness of who is seeing this patients is that working okay? And we're going to actually keep the group that formed this guideline together and meet…is it quarterly that we agreed to meet or twice?

Jaymie Mai: The full group will meet twice next year doing the pilot period. There is a subgroup off of that that will meet more often to look at the implementation, the evaluations of the pilot.

Gary Franklin: So we have a working group that's going to help us…all of the agencies…we didn't want the agencies just to go off and just do it without continuous feedback and support from the community of physicians that do this kind of thing. So I hope I answered your question.

Vyn Reese: I think so. I think we need a broader group than just pain management consultants.

Gary Franklin: It is broader than it was originally. It probably…it may not be quite as broad as, you know, some folks would like to see, but we couldn't do everything here and we couldn't get full agreement on every single point. So we did the best we can and the main thing now is, is there going to be enough to go around, you know, enough expertise to go around? Will people be available? Is it in rural areas, etc., etc.? There's important questions we have to answer from this pilot. That's why it's a pilot.

Siri Childs: Gary, may I just point out something to Dr. Reese? Did you see the description of the other consultants on page four?

Vyn Reese: That's what I read.

Siri Childs: Under special?

Vyn Reese: Right. Especially consultation. That list should be up at the front. That's what I read. I read the list on page four.

Siri Childs: Which you liked?

Vyn Reese: Which I liked. That's what I'm saying. The list on page four should be…instead of just pain management consultation it should be that list.

Siri Childs: Aw.

Vyn Reese: That's all I'm saying. The page on four should be the list…the same thing on page one. That's where it should first appear in the work.

Gary Franklin: Oh, I see. So you're talking about…you're not crippling with the list, you're crippling where it's at kind of…

Vyn Reese: I'm crippling where it's at because pain management consultation is not enough, it's not enough to guide somebody…

Gary Franklin: Right. So we're going to develop resources to go along with this guideline and we're going to have a web site. Is that right Jaymie?

Jaymie Mai: Yes. I do want to point out on page two that table. The specialty consultation, I guess, the way the discussion throughout the whole discussion was, you know, you can get a specialty consultation at any time regardless of the dose if you feel as a practitioner that, you know, it's not working whatever treatment it is and if you feel like there may be other conditions that haven't been identified or diagnosed that a specialty consultation is really…I mean you could get one even at doses less than 120, less than the threshold.

Gary Franklin: Okay. Thank you. These are the kinds of things that we've already spoken about including recognition and management of behavioral issues during opioid weaning, which again that's more in part two. If you're already inheriting a bunch of patients that are already on high doses that's part two of this guideline. The main emphasis of the guideline is as you're transitioning patients who are opioid naïve to start with. Dan?

Dan Lessler: Before we leave the specialist issue, you know, Gary what I would like then is a list of orthopedists in King County who see Medicaid patients, as well as psychiatrists who see Medicaid patients, and pain specialists who see Medicaid patients? That would be very helpful to me. I'm unaware of any at this point.

Gary Franklin: Well, that's a problem we're all facing and, you know, I don't know who they are, but we will develop at least a publishable list of people willing to see patients. Now whether they are willing to see Medicaid patients or not I guess we can check that out. But that wasn't, you know, we're not responsible for that. I can't be responsible as to whether any given physician is going to use their time in that way.

Dan Lessler: But I think...I understand that you're not responsible for it, but I think…I think the point is well taken. These people need specialty consultation, but it's not available. And I think, you know, for a large segment and certainly here as the DUR this is the population that we're most concerned with. So…and I'm glad that there will be follow up to assess availability and so forth and whether people are actually able to access these services. What I can tell you right now is that they…to the extent that this guideline is going to be effective in the Medicaid population it will depend upon having that access available and it is not available today.

Gary Franklin: Okay. Well, one thing I am thinking about although it's not related to this right now, but in the future I would like to see this kind of thing sort of linked to a more incentivized best practice type of thing. So, you know, it would be nice if we could figure out how to do this better in a year to say, "Okay, now that we figured this out it's really going to take big dividends in prevention of these horrible and maybe even in saving some money here to pay more for an appropriate intervention at these points." We're not there right now. We're going to have to demonstrate that this is sort of working, but that's what I'm thinking of. I'm thinking we might need to incentivize this a little bit more than we have and that's certainly true in the, you know, for the insurers that pay less.

Dan Lessler: Yeah, I agree.

Gary Franklin: I mean it's something that we couldn't solve in this effort here.

Dan Lessler: Right. And again…but again I think it's part and parcel of the problem. I mean I think, for example, I mean I know I've got patient's who are on chronic opiates who have degenerative joint disease who need hip replacements, who need knee replacements and you can't get them.

Gary Franklin: You can't get the replacements?

Dan Lessler: No. You can't…there is not an orthopedist who will see these patients. So it's, you know, it's a real…and actually I think the lack of access…you point out in the guideline that…and I think we've had some discussion here that there's often comorbid mental illness. I think a lot of times we're treating anxiety disorders with these medications and again, you know, I think part of that is you can't get access to mental health expertise. So there's…it's not just that you need the access to assess whether or not these drugs are needed and how they should be managed, you need access in order to avoid ever prescribing these drugs in the first place unnecessarily. Siri?

Siri Childs: Well, I was just going to offer from Medicaid that I know Jeff is working hand-in-hand with Gary on this issue and the example that we have while it's not as large scale as what we are talking about in the future, but we have built our second opinion network for the ADHD drugs and, you know, we're building on that network and we've given those folks an enhanced payment to see, you know, those folks as a second opinion. So we have kind of a model for Medicaid that I know Jeff will take forward to try to get funding for to help.

Gary Franklin: So it's a fairly legitimate concern. It's probably a little harder to do something about then…get the pain experts and getting agreement, but it sounds like there is vision at Medicaid to do something like this.

Again, part two the guideline for optimizing treatment…other parts of it are, you know, assessing treatment of patients currently above the dosing threshold, how to reassess opioid doses when higher doses are not working, possible referrals to pain centers, if necessary. Oh, the one interesting agreement, you know, I thought walking into this with all these guys that, you know, if you have patients that are on real high doses, you know, how long does it take to get them off or are you going to need, you know, other drugs like buprenorphine or a team and the answer from them was most patients, most patients you ought to be able to wean them relatively quickly and without these drugs and these teams. Even, you know, I know at the U they have used some pain cocktails to do this kind of thing and there was even push back on that idea. It's kind of dangerous to do it, it's unnecessary in most patients, but those are possibilities for treating the most difficult patients to wean. But the average patient in outpatient practice you ought to be able to wean if you think they're in trouble, you think they're not improving their function, you know, without that kind of a problem.

Next slide. Part two is aimed again if the patient's already on high doses and included are some sort of reasons to discontinue opioids or refer for addiction management, referrals for addiction management or opioid agonist treatment as we just said, and then additional resources. So this is actually more of a resource thing and we do hope to have…develop additional resources for doctors to use. For example we hope to have next year an opioid seminar or conference and part of that might be a "train the doctor" kind of thing for primary care people in the afternoon that they could develop some training on these things about how to better use opioids in chronic, non-cancer pain.

Also included are tables of specific dose threshold. One of our doctors, Hal Strockbridge, developed a kind of an automatic way to possibly be able to do it on line. Are we going to be using that, Jaymie?

Jaymie Mai: I think it's under development, but it's our hope to…when the guideline is published to have it available on the web site for practitioners to download to their desktop to use on a daily basis or how often it is that they need to. So we are working on that.

Gary Franklin: So, you know, we're planning on rolling this thing out probably in January and again we're going to have a monitoring committee more or less meeting twice in the next year. We're going to have a working group who will be meeting more frequently than that to help us design the educational pilot and the elements of it and the evaluation parts of it. We'll probably pull in at least one or two people from the University to assist with that…to do that evaluation as well because we want to take a hard look at this. So, you know, I think it's a soft landing kind of a thing. It's kind of a soft cap. It's a cap that's related to taking a deep breath if function has not improved and the whole purpose is to try to prevent the morbidity and mortality that we've seen and I think it's going to be a huge deal even though it's not setting any kind of a standard I think just getting this thing out there and having people thinking about when to start thinking about not raising the dose is going to have a big effect on primary care physicians. I'm really excited about this. All of the agencies have worked very hard. I want to thank all the pharmacy staff at the agencies and other staff that have been working hard on this like Levonda McHanlis who is a nurse in my shop. So if you have any other discussion points or questions we can talk about that now or you can email me.

Carol Cordy: Carol Cordy here. I was wondering…I can't remember how long ago it was that we talked about opioids with the committee and preferred drugs were methadone and morphine and what I'm wondering is it's been awhile since that happened. Has there been any increase in accidental overdoses?

Gary Franklin: I think that for the state data that we showed they can't tell which drug…is that right, Jaymie?

Jaymie Mai: I believe they can tell the drug and that the majority…I would say the most prevalent report is methadone although I am not…I mean the rate of increase happens before the…placing long-acting opioid on a preferred drug list before 60AA(?) and the preferred drug list.

Gary Franklin: But for L&I it's 32 deaths. They were half methadone and half oxycodone.

Carol Cordy: And we don't have numbers before that change to know?

Gary Franklin: Before the 1998…you mean before you did your thing or before the…

Carol Cordy: Yeah, before we did our thing.

Gary Franklin: That started increasing in '98.

Carol Cordy: No. I understand the increase before. I just wondered if there was any additional increase.

Gary Franklin: Yeah, I guess we haven't looked at that. Have you looked at that Jaymie?

Jaymie Mai: No. We didn't look at it…the problem…some of the problem is, is there is not a single opioid agent when you look at the death certificate. The report is a multiple…a lot of times there are multiple drugs involved and it could be a combination of opioids not a particular agent. So it's kind of hard to divvy out, you know, the particular.

Gary Franklin: There are patterns in these patients. The DEA did a report a few years ago on oxycodone deaths and they actually got stomach contents and stuff like that from the medical examiners and, you know, the common drugs that are…that accompany them are some benzodiazepines, but more commonly tricyclics…the kind of drugs you would use long acting opioid or short-acting opioid, a tricyclic. Maybe a sedative hypnotic to sleep at night. Those are the patterns that most common…

Man: Alcohol also?

Gary Franklin: No. As I said, we…our criteria for definite and probable…if alcohol was mentioned on the death certificate or if an elicit drug was mentioned on the death certificate we called it only a possible. So they weren't counted as definite deaths.

Woman: I was going to say that with most deaths it is a combination with opioids, antidepressants, benzodiazepine, sedative hypnotics and sometimes muscle relaxants and all that stuff. So it's a whole host of things—not a particular single agent.

Bob Bray: A couple of things. One is the first thing that struck me as I looked at this and there's a lot of good information in this guideline, I agree, but you state right up front that the purpose is to educate primary care physicians and by inference it implies that if you consider yourself a specialist this guideline doesn't apply to you and/or you don't need education about the management of chronic, non-cancer pain. So as a primary care physician I look at that and think, "Well, we can all stand to learn something." And even though I'm sure the vast majority of folks that are prescribing for patients under these agencies are primary care physicians because we're the ones that are willing to see them in the first place. You made that point earlier. That sort of hits me as being a little odd and I think it should be generalized. I think that, you know, you're really trying to get at those folks who are prescribing these drugs and I think whether they are primary care physicians or whether they consider themselves specialists it would seem as if you're differentiating this from folks who already treat patients with…who are pain specialists and that is understandable. So that was one thing that kind of struck me.

The other issue is you talked about what you intended this not to be and you intended it not to be a limit for narcotics, but because of what Dan's already mentioned I can tell you that that's exactly what this guideline is going to do without the access to people who are willing to do pain consultants. Because what practically is going to happen in Spokane. I'm in a town with 350,000 people, as well as Colfax and Pullman and Republic and everywhere else. Physicians may get to a point where they will say, "We're at a point of 120 mg of morphine equivalence per day. I can't get you a pain consultation. I can't give you any more medication than this." So in fact I think it is going to be a dose limit because of the access issue. So I understand that it isn't intended to do that, but I think the unintended consequence of how this is being done is it will be a dose limit on patients that are covered by these pairs.

I think that just as I'm sure if you sweeten the pot a little bit for pain specialists to see these patients that may get them interested in it. I would hope that that trickles to the rest of us who are actually taking the responsibility to deal with these folks because they can…this can be a tough thing to do. And we're not just doing a consultation, but we're available 24/7 to these patients to deal with their problems and we don't get paid enough either, but we're doing it. So I wanted to lodge that comment, as well. I know Vyn wants to say something.

Vyn Reese: I have two observations. One is the deaths that I've seen with opioids or that I know about have happened when you're changing from one opioid class to another like…especially going to methadone. I'd say methadone is a very tricky drug to use. It takes a long time between…to adjust the dose between doses. I've seen disasters happen when doctors have taken somebody off of oxycodone…long-acting oxycodone or long-acting morphine and put them on methadone and get the wrong dose or the wrong dosage interval. You should be looking…targeting changes. Okay? And especially a big jump in dose. I don't know if you can do that. I don't know if the pharmacies can target that sort of thing, but that's when the fatalities occur is when changing opiate classes, especially to methadone.

The other…and also escalating the dose too rapidly. Somebody who doesn't know how to treat pain patients, you know, escalates the dose too rapidly…big increases in dose and changes of opiate class are two major risk factors for accidental death.

The other thing you didn't mention here is gabapentin in the…consider prescribing opiates when other conservative measures haven't failed. The state made a huge crack down on lowering gabapentin prescriptions. Gabapentin is a very good drug for neuropathic pain and it was expensive

and that's when the crack down was made. As people are prescribing less gabapentin you may be seeing more opioid deaths as opiates are being used more. So I mean gabapentin is a relatively safe drug. It's great if they have neuropathic pain. Opiates and gabapentin have shown to be synergistic in that class of patients and I think that…and gabapentin is now a generic. So I think gabapentin should be mentioned in here. Every pain clinic I've ever sent anybody to said, "Well, is he on gabapentin?" That's the first thing they ask and, you know, my patients are usually on it if it's neuropathic pain.

Gary Franklin: Well, my recollection of the work we shared with you a couple of years ago…a year and a half ago on gabapentin was that that guideline was actually quite liberal on neuropathic pain, but it kind of hammered down on non-neuropathic pain. And among the uses for neuropathic pain my recollection is that the only reason there was any kind of a dosage qualification was because it just doesn't get absorbed much beyond a certain dose in the guide. So that was the only dosage thing, but for neuropathic pain the guideline was quite open and…

Vyn Reese: It just isn't mentioned in this outline and it's one of the…

Gary Franklin: So there might be some we add to the web site on that.

Vyn Reese: Right. Basically it's one of the bedrocks of treatment for chronic neuropathic pain, which is a big number of these patients.

Gary Franklin: That's a great point.

Vyn Reese: Anyway, those are my observations. If you can target, you know, huge dosage jumps, changes in class, and adding gabapentin, you know, I think those are all important parts.

Gary Franklin: I think those are good red flags.

Dan Lessler: I just noticed that it says final draft. Is there any chance of taking some of the input here to…

Gary Franklin: Well, again, we can implement these things without putting them in the draft because we haven't started yet. So I think these are great ideas…for example the red flag piece and we can add in the resources…the other resources that we develop, but we can't have another meeting with the…the pain management guys developed this and…

Dan Lessler: Can't take these sort of as a friendly amendment or something like that?

Gary Franklin: Just like you are, you know, we have to reimburse folks to participate in these things and so we've already, you know, expending quite a bit of resource to have these five meetings and we're going to have more meetings next year, but these are great points and we will make every effort to incorporate them in one way or another.

Dan Lessler: Do we have another minute here or do you need to…?

Gary Franklin: I have another couple minutes, yeah.

Dan Lessler: Jason or Alvin was there a comment here? Carol, did you have a comment?

Carol Cordy: I was just wondering where buprenorphine is going to fit into this picture?

Gary Franklin: Well, I think I mentioned earlier my thought originally when we started on part two, which is where that would fit in, you know, if you're already inheriting somebody on real high doses and you want to find a way to reduce it or wean them or add some other medications to help with that is where that came in and I thought they would end up adding much more on that, but they actually pretty much thought that, you know, that would not be that common that you would need to do that, but some of that's in there isn't it Jaymie?

Jaymie Mai: Yeah, it's under part two page 7 where we talked a little bit about under referral for addiction management or opioid agonist treatment. That's where they distinguish methadone clinical and also buprenorphine therapy. They didn't…they didn't feel that they could make a recommendation for off label use for pain in high risk populations because they felt there wasn't enough evidence there to do that. So they reserved that for addiction management.

Gary Franklin: Again, I want to emphasize the main purpose of this whole thing is to try to prevent unnecessary escalation in opioid naïve patients and in patients with chronic non-cancer pain as you're starting to transition from acute to sub-acute to chronic pain, you know, if that is happening. It's not…the main emphasis is not on, you know, stopping opiates on people that are already on high opiates. There is just some guidance in here as to ways to think about doing that if that's what you choose to do, but the main thing is, you know, trying to prevent the next cohort of morbidity and mortality here in the state. but would be nice. I know it's difficult because I've tried and it's hard, but I think that would help.

Jaymie Mai: There is a small equagesic table.

Gary Franklin: You don't know how many hours we spent on this. We spent probably half the time of the five meetings on opioid conversion tables and disagreements about the actual conversion doses. So we went back to this other broader approach in here.

Alvin Goo: Right. I guess not conversion, but conversion from one opioid to another.

Gary Franklin: There is a lot of emphasis, almost a black box warning on converting to methadone. I mean that's really the main problem here.

Jaymie Mai: I do want to say that we are developing the calculator that would allow a practitioner to enter whatever opiate their patient is currently on and then have that be converted to a morphine equivalent just to get an idea of what the opioid…the morphine equivalent would be. There is going to be references to various conversion probably pointing to, you know, what you folks have developed a while back. The document on conversions so there…we're going to try to make those kinds of things available on this web site and provide the tools for practitioners to use in converting. Converting is very hard. Like Gary said we spent a lot of time discussing conversion. There's no agreement to use to one single kind of tool to use and so…but we know…we need to provide some sort of tool to help practitioners do it in a safe manner. So there will be tables on the web site and reference to the U. I know the U and Harborview, Steve Riddle's group; do have some of those tables for the various long-acting opioids.

Gary Franklin: But the original detailed table that we had…one of the reasons we decided to back off of it to this other table that's in here is because of some disagreement with some of the numbers in what you guys use. So we didn't want there to be a disagreement there, you know, it seemed inconsistent across programs.

Dan Lessler: Okay. Thanks a lot. I guess the…I'm looking on the agenda. It says expected outcome to your board recommendations. I think you have a bunch of recommendations that have come forth. My question I guess at this point and I look to Siri , is this the kind of thing that you want a…are looking for a formal endorsement from us?

Siri Childs: I think it was very important to the committee, the statewide committee, and Dr. Franklin and Jeff Thompson that worked on this guideline and did all of the networking throughout the state to have a recommendation from the DUR board to adopt these as an educational pilot for at least one year.

Dan Lessler: I'll ask…is there a motion then to adopt these guidelines as an educational pilot for one year and then could…I would assume then that we will hear back then in terms of the evaluation at one year and how it is going? Bob?

Bob Bray: Bob Bray, again. When I look at the first page of the draft I don't understand that it's a pilot and I don't understand that it isn't education. All I understand is that it's a guideline and guidelines to me indicate there's a consequence for not following it. Now it sounds like you've not developed

consequences at this point for not following it. I think there are medical legal consequences of not following it. So I guess if that's really what it's going to be I'd like to see that the front page says inner agency, educational pilot guideline so that it's clear that this is the beginning and it may take a little bit of frustration off of the physicians if they find that they can't adhere to the guideline because of access issues.

Siri Childs: You can also make that very clear in your recommendation to our…to Medicaid that this is to be an educational pilot and you want to see a follow up and an evaluation in one year.

Dan Lessler: Okay. Any other…

Gary Franklin: Jaymie, do you have any comment on that? We did talk about that.

Jaymie Mai: Not really. I mean it's something that I don't think the committee…

Gary Franklin: I mean the committee did raise that same issue and I think it came up in the public hearing, too. So we do need to address that and do something about it.

Jaymie Mai: Right.

Gary Franklin: I think, you know, even the link to it on our web page should be to the educational pilot for opioid dosing or something. It should be called that, you know, on the web site and then whenever and however we send it out the type, you know, in the cover letter or whatever should be, "This is intended as an educational pilot."

Dan Lessler: Thanks. So with that do you want to actually make a motion? Would you feel comfortable in terms of your own?

Bob Bray: Well, I would move that we…that you proceed with it in that…with that caveat that it be designated as an educational pilot. That it's clear from the draft, the final draft that it is an educational pilot and then that we would request follow up in one year particularly not only for the positive results that are in…hoped to be intended from this, but also what benefits are there for access.

Man: Or perhaps as you said before unintended ill effects.

Bob Bray: Correct.

Angelo Ballasiotes: How about a requirement instead of a request.

Dan Lessler: It's a requirement to come back in a year with the evaluation? Okay. Is there a second?

Angelo Ballasiotes: I would second that.

Dan Lessler: Okay. Any further discussion. All those in favor say, I.

Group: I.

Dan Lessler: Opposed, same sign. Okay. Great. Thanks a lot.

Gary Franklin: Thanks very much for your input.

Dan Lessler: I appreciate it. Okay. So I guess…

Siri Childs: This is informational only, but I think you're going to be very pleased with the information. I mean you probably won't be pleased, I don't think. I shouldn't have said that.

Dan Lessler: It will further inform the discussion. That's great. So Scott Best, I guess.

Scott Best: Yeah, in conjunction with the opioid dosing guide and I'm going to start off there. On page 8 of the opioid dosing guide that you guys have in your handouts there is an equianalgesic dosage table for converting opioid therapies and I had looked at…I was asked to look at Medicaid patients and determine a few indicators based on what morphine equianalgesic dosage they were getting per day. And the way I calculated the morphine equianalgesic dosage per day is based on the table that's there if they had…if they were getting for instance hydrocodone—30 mg of hydrocodone is equivalent to 30 mg of morphine. So it would be a 1 to 1 conversion and if they were getting something else like codeine; codeine would be then converted at whatever milligrams they would be getting in codeine would be multiplied by 30 over 200 to get me my morphine equianalgesic dosage for the amount that they were getting and then I would multiple that by the number of pills that they got and then when I was calculating for the clients that we have I also looked at chronic versus cancer and Hospice, end of life type pain. So if they had a cancer diagnosis in the previous six months then they were not included in the graphs that you're seeing right before you, and if they had any Hospice claims at all then they were not included and if they were in a nursing home during that period they also were not included. The only clients that I included were ones that had at least 90 mg of morphine equianalgesic dosage per day over a period of three months. And so then I averaged over that three months exactly what they were getting for that three-month period and the graph in the upper left hand corner is the drug and alcohol related diagnosis episodes per client by morphine equivalent dose per day and this is also in your guide. It's under the HRSA data on the next page. I found that…I worked for Patient Review and Restriction for HRSA, which is a federally mandated utilization program that is for health and safety of clients. And so a lot of times when we're looking at clients and their utilization we're concerned that they might be going to multiple doctors and getting medications that are going to harm their health and one of the things we often look at is drug and alcohol diagnosis episodes and in this case we compared the drug and alcohol related diagnosis per client and among the group that was 91 to 119 there was significantly lower percentage of them had drug and alcohol related diagnosis and then when they got above 120 to 179 it went up and then 180 and above it continued to rise. And so that was one of the things we looked at to see what affect the different morphine equivalent doses would have on their…on the number of claims that they had for certain diagnosis.

And then the second one to the upper right corner is the counter clients who died while being treated for chronic pain. And of course chronic pain they had to be being treated for at least three months and not have a cancer diagnosis or Hospice or nursing home and the ones that were 91 to 119 there were no deaths, 120 to 179 there were no deaths, and then 180 plus there were 19 deaths among this group of people. This is claims for three months and so 19 of those people who were getting the above 180 mg dose per day died during that period. I don't have what the cause of death was because that's not included in our claims data, but we do know that the deaths were higher among that group than they were among either of the other groups.

Also I was asked to look at, within that 180 plus, where the deaths occurred and between 180 and 200 four deaths occurred and it slowly tapers off from there down to the upper limit of clients who were being treated for chronic pain. Right at 180 you start seeing deaths.

Then the account of clients that were in the group there was about 3,600 clients that we…that actually got at least 90 mg of morphine per day over a three-month period and the vast majority of those are in the 180 plus group, 2,739 of them are in that group. The 120 to 179 group there were only 605 of them, and the 91 to 119 group there were 247 of them. So we're having quite a few clients that are getting treated for chronic pain at doses above 180 mg per day.

And then the last thing that we looked at was a psychiatric diagnosis episodes per client by morphine equivalents and that also…the things that we look at in-patient review and restriction is we're always looking at quality of life issues. And so if we're not improving their qualify of life then we're always concerned about that and in this case psychiatric episodes…psychiatric diagnoses and drug and alcohol related diagnoses can sometimes be indicators of those things. Psychiatric diagnoses are higher among the group that is getting 180 plus and it's lower among the 90 to 119 and of course it is just stair steps as you go up. These are the numbers that we came up with and we thought that they were indicative of some of the quality of life issues that these clients face when they are being given such high doses.

Dan Lessler: Okay. Thanks.

Ken Wiscomb: Ken Wiscomb. We see a number of folks in our clinic system that use multiple narcotics and I think we've noted anecdotally that the higher the dose for these folks the more likely it is that they have multiple prescriptions and they are seeing multiple providers. When you…this block of 180 plus did you have a way of differentiating those folks when you did that study? And was this by actual patient? Or was it by script? In other words does it take into account people who might have multiple prescriptions?

Scott Best: Oh, the way I determined how much they got…this was averaged over a month and then there was a three-month period they had to have greater than a 90 for all three months in this period and then I took their average over the three-month period. And so what I did is I added up all of their morphine equivalents for all of their prescriptions, came up with a total morphine equivalents for the three-month period and then divided it by the number of days in that three-month period. And that's the common way that we come up with calculations when we're looking at these things.

Vyn Reese: This is Dr. Reese. It's interesting that the vast majority of the patients were getting more than 180. I mean very much smaller numbers were getting less and you're wondering if…if in psychiatric conditions and drug and alcohol abuse are also more common at that number. So it's like it's hard to know what was first, the chicken or the egg? Also, how much of this is untreated pain, too? You don't know that. Somebody may have been escalating the doses on patients for untreated pain and you would think that psychiatric problems would have arisen at that level, too. And if they are patients like, you know, as we talked about earlier who can't get their pain treated like can't get a hip replaced or something else that's another issue. It raises a lot of questions more than a lot of answers as to why this is so. The logical thing is that more patients in that group are chronically drug addicted or drug seeking and also have major psychiatric illnesses. None of those things are easy to treat and there are not enough referral services to treat them all. The thing I think we really need to cut down on is multiple prescribers giving multiple prescriptions to these patients and adding to the problem with no controls. And I know we've been working on that, but that's part of a really critical piece of this is to stop that practice. And so providers know what's happening and can figure out that the patient seeing 10 other doctors is getting 10 other prescriptions and that's why it is adding up to that number.

Scott Best: Right. And that's the focus that I'm getting, too…that we're working with. The inpatient review and restriction we have specific criteria and one of those criteria is they would have to get…narcotic prescriptions would have to be from four different prescribers in order to meet the criteria for us to look at them and so…or they would have to be going back and forth between at least two prescribers who are going…who are giving them routine prescriptions and then they would meet our criteria in which…then we would look at whether it was medically justified or not and then we would look at whether it was safe or whether it was endangering the client. And so, you're right, that's one of the things that we're always looking at. Also one of the things that I found is that…among the…we just combined with the mental health resources and one of the things that they say is whenever they have a client who comes in who is addicted to substances, to chemicals, and also has mental health problems they cure the addiction first and sometimes the mental health problems will just go away because they are caused by the fact that the client is getting so much medications and narcotics and things like that.

Angelo Ballasiotes: You got me going there. This is a two-legged stool and sometimes a three-legged stool. You've got to treat them simultaneously or you're not going to have a very good success, number one. Number two, you might have some personality disorder in there also. So you wind up re-raising these people. So it is a very difficult issue to deal with, but I disagree with getting them off the drug because you're not going to do that without treating them simultaneously for the mental issue. And it's already been brought up that there's a lot of anxiety and these people don't understand it sometimes. They don't understand why they are taking the medication that they are and they are not getting the relief that they thought they would be getting or receiving. It is a very difficult issue to deal with.

Scott Best: Yeah, when I first got involved in this I had some thoughts about what a client who was…had five doctors would look like. I thought that they would be a client who was living, you know, well off

the land. They would have multiple fancy cars because they are, you know, a lot of these clients couldn't possibly be taking all of the narcotics that they are getting and they don't have any diagnoses that would prompt them to be getting that much. And they are going to lots of providers and so I always thought, you know, these guys are really doing well. They're probably living in fancier houses than I am and stuff. That's never the case. Every time I see one of these guys it's like they are…we've ruined their lives by allowing them to take these medications and it's like I just feel so much different about this, you know, and I've heard from providers. I've heard that there are providers who have said that we are ruining…when we prevent a client from going to multiple providers when they are getting narcotics like that we're killing their second form of income. But that's not what I see. I see clients who are miserable because they are getting all these narcotics and maybe they are trading it for cocaine or something else, and they are really having a rough time. It's awful.

Man: Just following that thought for a minute though…I don't know how long it was, Sherry could probably remind us, but I think about 2001, one of the first times Dr. Franklin came to the predecessor of this committee, the year that Oxycontin had come out he had grave concerns because it suddenly represented the first year a huge amount of their budget…much more than they expected and Siri ran, as I remember, a study…we looked at the amount of narcotics above a certain level of morphine that were written in the state and by, you know, by what prescribers, how many people were getting multiple and it figured out that…and I'm remembering this, but if you did it on a bell curve the end of the bell curve was about 120 mg and there were very few outliers beyond that.

Siri Childs: Oh yes, I remember the study.

Man: Do you remember? We were very surprised because we had started out with the opposite premise, but I guess my point is that now you're talking about being a little bit reluctant to tighten that less…for providers and I'm thinking to myself, "Gee, if we saw a bell curve that was 120 or less three years ago and now we're seeing a bell curve that…where the majority is 180 mg or more, maybe we're not being tight enough."

Siri Childs: Yeah. It's all about resources. It's all about resources. You know, Scott and his group can only do so much for so many of the clients. So we try to do as much as we can with the resources that we got. I do remember that. We were trying to look at a dosage limit for Oxycontin and we agreed to 320 mg of Oxycontin and Scott I don't know if you can run that through your computer quickly to know what that morphine equivalent dose is, but it's got to be pretty incredible. And at the time we looked at…we used main…a methodology from Maine Medicaid, the state of Maine, and ran it…our clients through it and I think it was like 92% of our clients fell under 320 mg of Oxycontin and so we knew that we had the resources to handle the 8% if we blocked it at that point.

Scott Best: It was 120?

Siri Childs: It was 320.

Scott Best: Yeah, that would be 480 or a little bit more than that.

Siri Childs: That was our first attempt to do some kind of a block. Do you all want me to tell you how many Oxycontin users we have in Washington now a days?

Scott Best: Sure.

Siri Childs: You're going to be just amazed because when we started the preferred drug list with the long-acting opioids Oxycontin represented 70% of our utilization. Today, the statistics that I looked at…November is out, but I've only seen October. We're down to less than 3%, you know, of our clients. And if you think that's a good story I gotta give you another really good story. Do you remember the old DUEC? When you gave us instructions to not approve carisoprodol…do you remember that we had over 4,000 patients in Washington on carisoprodol? Do you want to take a guess how many we have today? We have six.

Angelo Ballasiotes: You know, most people don't realize that drug metabolizes to meprobamate and that's why they like it.

Siri Childs: We have six patients only thanks to your recommendation and us moving them to something that's just as effective and safer.

Vyn Reese: Propoxyphene out to be another target. I saw that listed in the opiate guideline. Darvon is a terrible opiate. It's a very dangerous drug and overdose…it's a mild analgesic. I mean it's a worthless drug. It's very dangerous and it causes euphoria so a lot of people abuse it. So it's like…

Siri Childs: Give us some direction guys.

Vyn Reese: Well, we talked about that before. It's another one that probably needs to go.

Dan Lessler: Okay. Does that pretty much get us through our agenda?

Siri Childs: Yeah.

Dan Lessler: We appreciate the presentation and information. It's helpful as we continue our discussion around usage of opiates in chronic pain. So I guess if there's no other business then we can adjourn. Thanks.

Siri Childs: I'll also be emailing you your assignments for the DUR annual report.

Vyn Reese: Do you have the annual list of meetings for next year? That is coming out?

Siri Childs: I'll make sure and send it all out to you.

Vyn Reese: I want to make sure I get that. Thanks.

Siri Childs: Yeah. I may have a special surprise for all of you this year, but I'm not going to tell you yet.